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HEPARIN TREATMENT OF PATIENTS WITH ANGINA PECTORIS*

Failure to Influence Either the Clinical Course or the Serum Lipids

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THE treatment of angina pectoris for many years has been directed toward relief of the heart pain either by increasing the caliber of the diseased coronary arteries or their collaterals with vasodilators or by reducing the work load of the heart. The concepts relating atherogenesis to a defect of lipid metabolism have led to more ambitious therapeutic attempts to halt or even to reverse the development of atherosclerotic lesions in the vessel walls. After an association was found between elevated serum cholesterol levels and the precocious development of coronary atherosclerosis,[1-3] efforts were made to reduce the serum cholesterol levels, with the hope of preserving and improving the myocardial circulation. Restriction of dietary lipids[4] and treatment with lipotropic agents[5, 6] have been tried for such purposes. These relatively short-term experiments with man have been equivocal or have failed to demonstrate beneficial effects.

Gofman and his co-workers[7] have reported their conclusion that a significant positive correlation exists between atherosclerotic disease and high serum levels of certain classes of lipoprotein molecules as measured in the ultracentrifuge. Graham et al.[8] subsequently demonstrated that the parenteral administration of heparin resulted in immediate changes of the lipoprotein composition of the serum without affecting the serum lipids as measured chemically. Data confirming these transitory effects of heparin on serum lipoproteins have been published,[9] and it has also been demonstrated that the synthetic anticoagulant Treburon,§ when administered by the transbuccal route, has a similar action on the serum lipoproteins. In addition this medication lowers the level of the serum total cholesterol and phospholipid.

Graham and his co-workers[8] reported that parenteral administration of heparin inhibited the development of atherosclerotic lesions in cholesterol-fed rabbits that, judged on the basis of a parallel control series of animals, were expected to show such lesions. In addition these investigators described a dramatic effect of the treatment in alleviating the frequency and severity of heart pain in 55 of 59 patients with angina pectoris. A detailed description of the method of evaluation used in this study was not presented.

Subsequently Engelberg[10] reported favorable clinical results similar to those of Graham. In contrast Russek et al.[11] and others[12-15] found heparin ineffective in the treatment of angina pectoris. An experiment carried out to evaluate the effect of heparin upon the clinical course and the serum lipids of a group of patients with angina pectoris is described below.

METHODS

Patients with a characteristic history of angina pectoris were selected for this study. Angina pectoris was defined as paroxysmal, substernal pain of limited duration brought on by exertion alone or by exertion and emotional disturbances, and promptly relieved by rest or nitroglycerin tablets. Patients with other causes for chest pain were excluded from the series unless they were able to distinguish clearly the pain of angina pectoris from that of other causes. The selection, clinical management and observation of these subjects were made by one of us (H.L.C.).

Twelve men and 1 woman ranging in age from thirty-four to eighty-one years, with angina pectoris of two months' to six years' duration, were the subjects of this investigation. Although 13 subjects were studied, 14 courses of treatment were available for evaluation since 1 of the subjects entered the study a second time after a two-month interlude for a transurethral prostatectomy. None

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§Treburon is the sodium salt of sulfated polygalacturonic acid methyl ester methyl glycoside.

of them were engaged in full-time, gainful occupation. The subjects were studied for periods extending from 7 to 13 months in a hospital outpatient department. A complete physical examination, x-ray examination of the chest and electrocardiogram were done on each. Although all subjects showed abnormal resting electrocardiograms, two-step tests with electrocardiograms as standardized by Master et al.[16] were performed repeatedly in 9 cases during the course of the study. After exercise, pain and changes in the electrocardiograms consistent with myocardial anoxia developed in 7 subjects. One subject had pain without electrocardiographic changes, and the other demonstrated neither electrocardiographic changes nor pain.

The subjects were observed for 1 to 4 weeks before the institution of any therapy. During this time examinations were completed, and the severity of angina pectoris was estimated. The subjects were familiarized with the simple report cards provided; these were similar to those described by Greiner et al.[17] The cards were used by the subjects to record daily the severity of the symptoms of angina pectoris. Opportunity was provided to describe the heart pain each day as "usual," "worse," "very bad," "better" or "no attacks" by a check mark in the appropriate block on the report card. The number of nitroglycerin tablets* used each day was also recorded.

After this preliminary period of examination all subjects received 10 cc. of a placebo intravenously twice weekly at intervals of 3 or 4 days. The placebo used was a 5 per cent solution of glucose in water. For the first week of the placebo treatment the clinician knew what medication the subjects were receiving, but the subjects were led to believe that they were receiving possibly effective therapy. At varying times thereafter, which were selected at random, 100 mg. of heparin† dissolved in 10 cc. of water was substituted for the placebo by an assistant. The time of this substitution was not known to either the subject or the clinician. During the last 2 or 3 months of the study clinic visits and treatments were arranged on a weekly instead of a semiweekly basis. Examination of the data disclosed no change in any subject's course as a result of this modification.

*The tablets used contained 0.4 mg. of nitroglycerin.
†Kindly supplied by the Upjohn Company, Kalamazoo, Michigan.

The preliminary periods of placebo administration were continued for 10 to 91 days in various subjects for a total of 867 subject days of this treatment. Heparin treatment was then given over periods of 28 to 151 days for a total of 1329 subject days or a mean of 95 days per subject. All except 3 subjects received heparin treatment twice weekly throughout the entire period of its administration. In these 3 the heparin treatment was given twice weekly for intervals of 18, 80 and 80 days and thereafter once weekly for 84, 32 and 25 days respectively. All the subjects except these 3 and 1 other were observed during another post-heparin period of intravenous placebo treatment administered either once or twice weekly for periods ranging from 25 to 168 days for a total of 1117 subject days.

At every clinic visit the clinician questioned each subject, and noted the relation between the heart pain and the subject's activity and environment. During the preliminary period before parenteral treatment was started, blood was drawn from each subject for serum lipoprotein determinations, performed by the method described by Gofman et al.,[7] and for analysis of serum total cholesterol, by the technic of Abell and her associates.[18] At intervals of approximately a month thereafter, and just before the administration of the intravenous therapy of that visit, blood samples were taken for repetition of these measurements. Initially a modified Lee and White clotting time[19] was measured with this blood, but because no abnormalities were found during the first several months this procedure was discontinued.

TABLE 1. *Sample Periods Chosen from the Total Course of Therapy of Each Subject.**

TREATMENT	INITIAL PLACEBO		HEPARIN		PLACEBO AFTER HEPARIN
Average duration of treatment	62 days for 14 courses		95 days for 14 courses		112 days for 10 courses
Period	1	2	3	4	5
Sample	1st 28 days	Last 28 days	1st 28 days	Last 28 days	Last 28 days

*For each subject there was a variable interval of continued treatment between the first and second, the third and fourth and the fourth and last sample periods.

RESULTS

Clinical Evaluation

For the purpose of clinical evaluation, consideration was given to the following classes of collected data: the subjects' oral reports; the weekly nitroglycerin intakes computed from the subjects' daily records; the percentage of "better" and "worse" days so far as chest pain was concerned, as computed from the subjects' report cards; repeated two-step tests; and a judgment of the clinician based on an analysis of all the information available.

To facilitate presentation of the results of this experiment, samples of the voluminous data available were considered. For this purpose the total

time of treatment for each subject was divided into the three major periods of initial placebo therapy, heparin therapy and post-heparin placebo therapy. As indicated in Table 1 the sample periods chosen for evaluation were the first and last 28 days of both the initial placebo therapy and heparin therapy, and the last 28 days of placebo therapy after heparin (Table 1).

Subjects' oral reports. During the course of the study, 11 of the 13 subjects were enthusiastic about the improvement they experienced. Several reported relief from anginal attacks at night, most were impressed with the decreased frequency and severity of pain, and many believed that their tolerance to exercise had increased. Of the 11 subjects who described improvement at some time during the study, 7 reported consistent, progressive relief starting within the first four weeks of placebo treatment. Two additional subjects stated that they felt appreciably improved later than the first month but still this improvement occurred during their initial periods of placebo administration. Two subjects first experienced relief during the time they were receiving heparin intravenously. In one of these subjects heparin was started after only 18 days of placebo treatment.

In all subjects, regardless of when improvement was first experienced, it continued for the remainder of the total period of observation. There were fluctuations from time to time in the degree of relief, as expressed in interval interviews, but there was no sharp change for the better associated with the introduction of the heparin treatment. The subjects' oral reports indicated that they were unable to discriminate between placebo and heparin treatments by symptomatic improvement.

Nitroglycerin intake. The subjects' professions of relief from pain were supported generally by evidence of decreased nitroglycerin intake. However, these professions of improvement often did not coincide with decreased need for this medication. Although there was wide individual variation in the range of decreased nitroglycerin consumption, even in subjects with about the same initial level, all subjects reported more or less regular decreases of requirement for this medication.

Figure 1 shows the changes in the number of glyceryl trinitrate tablets used weekly during the sample periods of Table 1. Most subjects had obtained maximal relief as judged by this criterion during the preliminary period of placebo administration. There was little evidence of any additional benefit attributable to the heparin treatment.

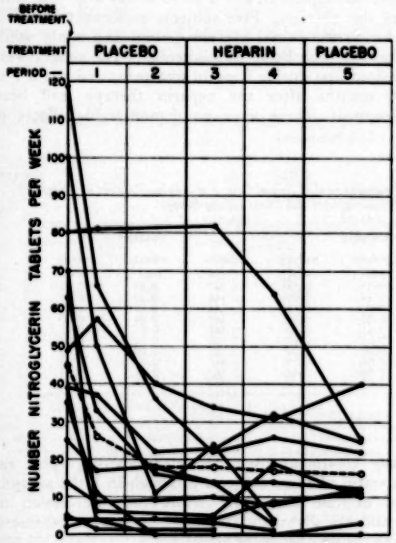

FIGURE 1. *Influence of Placebo or Heparin Treatment on Each Subject As Reflected by the Recorded Weekly Intake of 0.4-Mg. Tablets of Nitroglycerin.*

The broken line represents the mean response of all 14 courses of treatment. The curve starting at 80 describes the subject in whom periods 1 and 2 comprised only 18 days.

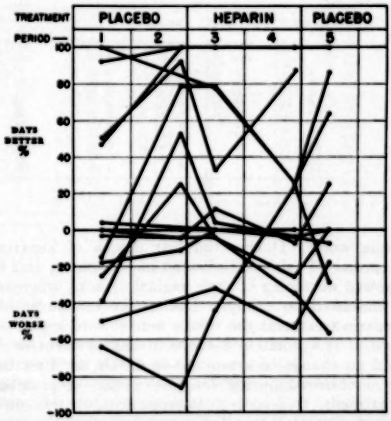

FIGURE 2. *Influence of Placebo or Heparin Treatment As Reflected by Each Subject's Daily Report of His Condition.*

The percentage of days of improvement as positive were added algebraically to the percentage of days of worsening as negative, without weighting for degree of change.

Report cards. The report-card data were evaluated after the subjects' interpretations of their condition had been condensed into two classes. For this purpose the number of "better" and "no attack" days were summed as one class (positive), and the "worse" and "very bad" days were summed as the other (negative). No weighting was introduced to describe the degree of change, and the days reported as "no change," which are not here considered, constitute the remainder of the exposure days.

To demonstrate trends of response with changes of treatment a diagram using the data from the sample periods described in Table 1 for all the subjects treated was constructed (Fig. 2). In 8 of 14 courses of treatment improvement was reported during the initial placebo period. In 2 there was no change of symptoms, and in 4 the condition became worse. During the first month of heparin treatment 4 subjects indicated improvement, and 4 showed worsening of their anginal attacks, whereas 6 indicated no change. During the remainder of heparin treatment the trends were toward aggravation of symptoms in 8 subjects, improvement in 2 and no change of symptoms in 4. Of the 10 subjects observed during the final period of placebo treatment, 6 described improvement, 1 was unchanged, and 3 reported worsening of their condition.

The data of the 10 subjects who completed all three periods of treatment were considered in detail (Table 2). There were available 632 subject days of initial placebo treatment, 984 subject days of heparin treatment and 1117 subject days of post-heparin placebo treatment.

The ratios of the "better" days to the total days of exposure were computed for each subject and for each of the successive treatments. Subtraction of these ratios for the initial placebo treatment from the heparin treatment and for the last placebo treatment from the heparin gave differences that were then evaluated by the use of a conventional "t" test. The same procedures were applied to comparisons of the influence of the treatments upon the observed frequencies of "worse" days. With the exception of a diminished frequency of "worse" days in the heparin treatment period ($t = -2.40$, $p < 0.05$), all comparisons revealed differences attributable to sampling variation with probabilities of 5 per cent or more.

Two-step tests. Twenty-six "two-step" tests on 9 subjects were performed at intervals during the study. The tests during the heparin phase of treatment were carried out from 4 hours to 2 days after the last injection, and 3 to 16 weeks after the start of this therapy. Five subjects underwent the tests during the initial placebo period and again while heparin was being administered. The others were tested first during heparin treatment and again 1 to 4 months after the heparin therapy had been stopped. There were no demonstrable effects of any treatment upon the electrocardiographic responses of these subjects although in 1 the amount of exercise completed before the intercession of pain was slightly greater during heparin treatment than it was before or after.

Total clinical evaluation. An evaluation was made on the basis of an analysis of each subject's course utilizing all the available data noted above, and modified by a knowledge of intercurrent environmental factors influencing each subject's condition. The analysis was made originally without knowledge of the therapy schedule. By this evaluation 8 subjects experienced definite improvement during the experiment — a generally progressive reduction in the frequency and severity of heart pain and greatly reduced nitroglycerin requirements. On subsequent comparison with changes of therapy the rate and degree of improvement was found not to have been influenced by the change from placebo to heparin or from heparin back to placebo treatment. Sharp changes, for either the better or the worse, lasting from a week to a month or more were often related to various mental, physical or environmental factors.

TABLE 2. *Evaluation of the Influence of Placebo and Heparin Treatment on the Clinical Course of Angina Pectoris as Judged by the Daily Report Cards of 10 Subjects Who Completed All Phases of the Study.*

Subject No.	Placebo			Heparin			Placebo		
	days total	worse total	better total	days total	worse total	better total	days total	worse total	better total
1	77	0.23	0.21	98	0.15	0.19	147	0.29	0.21
3	18	0.50	0.00	84	0.44	0.00	168	0.29	0.00
4	20	0.05	0.70	151	0.01	0.54	56	0.02	0.57
6	87	0.20	0.07	98	0.01	0.00	147	0.04	0.00
7	91	0.34	0.47	98	0.11	0.62	147	0.05	0.86
8	52	0.10	0.06	91	0.25	0.09	25	0.52	0.00
9	70	0.04	0.93	84	0.00	1.00	63	0.00	1.00
10	84	0.26	0.20	98	0.04	0.03	147	0.02	0.00
11	42	0.74	0.00	84	0.36	0.64	63	0.33	0.31
12	91	0.13	0.18	98	0.08	0.87	154	0.11	0.65

One subject became ill on the 56th day of the final placebo treatment and died 14 days later. He had previously received heparin treatment twice weekly for a period of 115 days. The clinical diagnosis at the time of death was myocardial infarction complicated by pulmonary infection. No autopsy was performed.

No hemorrhagic complications or other untoward side effects resulted from the intravenous administration of 100 mg. of heparin twice weekly for periods up to 151 days to these ambulatory patients.

Laboratory Results

The lipoprotein and cholesterol measurements on the serum of these subjects were studied according to the treatment periods (Table 3). For this purpose the values obtained during each treatment were averaged for each person. Inspection of data for individual subjects, as well as the tabulation of the means of all subjects for each treatment period, gave no evidence that the heparin treatment led to any significant changes in either the serum cholesterol or any class of serum lipoproteins measured. Blood was always drawn for analysis 3 or 4 days after the last injection of heparin. With intravenous injections of 100 mg. of heparin twice weekly there was no persistent effect on these lipoprotein classes for the interval of 3 or 4 days between injections, nor was any cumulative effect from prolonged treatment identifiable.

more, since each patient demonstrates a different combination and extent of these devious factors, comparing one patient with another or a grouping of them may lead to erroneous conclusions. Because of this variability from patient to patient, in studies of the effect of treatment on the manifestations of angina pectoris, some knowledge of the range of reaction of each patient must be known to the investigator, and each subject should serve as his own control. No single criterion of condition appears to be an adequate measure of the effect of medication, and some criticisms may be directed toward each of those proposed.

The use of report cards, as discussed by Greiner et al.,[17] was found to have certain definite limita-

TABLE 3. *Average Serum Lipoprotein and Cholesterol Levels of Subjects with Angina Pectoris during 14 Courses of Parenteral Treatment with Either a Placebo or Heparin.*

Subject No.	S_f12-20			S_f20-100			Cholesterol		
	Placebo before heparin	Heparin	Placebo after heparin	Placebo before heparin	Heparin	Placebo after heparin	Placebo before heparin	Heparin	Placebo after heparin
	mg./100 cc.	mg./100 cc.	mg./100 cc.	mg./100 cc.	mg./100 cc.	mg./100 cc.	mg./100 cc.	mg./100 cc.	mg./100 cc.
1	66.0	94.0	73.3	132.0	202.0	154.0	317	336	303
2	38.5	44.5	—	41.0	51.5	—	216	228	—
3	69.5	46.7	51.0	267.0	174.0	171.0	280	216	228
4	46.0	45.6	56.0	50.5	41.0	28.0	206	197	171
5	13.0	10.5	—	24.5	13.5	—	158	157	—
6	29.8	43.0	37.3	43.0	69.0	82.0	283	299	295
7	46.5	36.5	42.0	97.0	92.5	86.0	190	179	188
8	79.7	91.0	110.0	115.0	139.0	108.0	269	311	294
9	50.2	78.5	71.0	130.0	145.0	350.0	219	280	287
10	45.0	38.2	39.0	60.7	44.0	45.0	282	296	279
11	20.3	27.0	31.0	54.7	53.0	50.0	276	299	274
12	52.3	60.5	53.5	150.0	110.0	114.0	230	250	248
13*	32.5	29.0	—	116.0	72.0	—	261	243	—
14*	37.3	39.0	—	164.0	67.0	—	263	252	—
Means ± Standard Deviations	44.8±18.4 50.5±17.9†	48.8±24.2 56.0±23.9	— 56.4±23.4	103±65.2 110±67.5	90.9±55.4 107±36.7	— 119±93.4	247±44.1 255±40.8	253±53.5 266±53.1	— 257±46.8

*Subject No. 13 and 14 was the same person, observed during two separate courses.

†The data of the 10 subjects who completed all 3 phases of treatment.

Discussion

There is general acknowledgement of the difficulties involved in evaluating the effects of any therapy in angina pectoris. Psychic, somatic and environmental factors may alter susceptibility to pain, each in varying degree and direction. Furthermore, each subject was asked to record his current condition as the study progressed, using his "usual" status before the trials started as a standard of reference. Even during the preliminary period before treatment most subjects reported many more days of "worse heart pain," "very bad" or "better" days than those of "usual heart pain," indicating considerable variability from day to day. A "usual" status was thus recognized with difficulty. Though this record may be expected to have some relative value, the standard of reference of many subjects became blurred as the study progressed. There was often a tendency for the subjects to magnify the severity of the past distress in their recollection. There was reason to believe that they did not use their pre-study condition for reference each time the cards were marked although this was emphasized to them repeatedly. It appeared that they compared each day with a general impression of how frequent and severe their heart pain had been a few days or a few weeks before.

The advantages of simplicity and apparent objectivity of this method of evaluation are vitiated by the unreliability of the basic data. Since these data are easily reducible to quantitative terms, they are readily susceptible of statistical handling. As noted above, because of the many variables among subjects, such a manipulation may compound the errors and lead to a false conclusion, elaborate as the statistical treatment may seem. If the daily condition reports have any validity, the improvement indicated by the significantly fewer worse days occurring during the period of heparin treatment reflects merely the benefits conferred by the procedure of the study itself.

The course of weekly intakes of nitroglycerin tablets was probably the most accurate single measure of condition change since the vagaries of memory were not introduced and the perceptions leading to nitroglycerin medication may be expected to be relatively constant. This conclusion is limited by the assumption that such patients take nitroglycerin tablets only when they have chest pain. The nitroglycerin intakes (Fig. 1) were the most consistent of the measures and served to demonstrate that the first treatment in such an experimental plan occupies a unique position of favorability of response. A failure to recognize this experimental artifact might easily lead to incorrect conclusions in the evaluation of a treatment. Four subjects indicated both by their verbal estimates and by report cards that their conditions progressively improved well into the post-heparin placebo period. The rate and extent of this decrease in anginal pain is shown for each subject in Figure 1. If these curves were drawn on a weekly basis, they would generally be irregular and would vary in slope and time of flattening out. Neither the extent nor the rate of change described by such curves appeared to be altered by the substitution of heparin for placebo. About 100 days of parenteral therapy elapsed for most of these subjects, previously treated in a general medical outpatient clinic, before they achieved maximal improvement. This improvement appeared to be independent of the kind of treatment. The striking improvement in most cases while the subjects were on placebo treatment emphasizes the importance of frequent visits to an interested physician and the powerful effect of parenteral therapy in this disease.

The "two-step" tests done during the course of the treatments did not indicate a beneficial effect of heparin treatment upon the manifestations of angina pectoris measured by this test.

Treatment twice weekly with 100 mg. of heparin intravenously did not demonstrably alter the serum lipoproteins or cholesterol. Previous studies[8, 9] have revealed that such a treatment does lead to a transitory reduction of the S_f20-100 and S_f12-20 classes of lipoprotein in serum. The present studies indicate that there is no cumulative effect of serial intravenous treatment with heparin when this is administered at intervals of 3 or 4 days. The anomalous results of Rinzler et al.,[18] who observed "significant" reductions of certain classes of serum lipoproteins with placebo treatment but not with heparin treatment, is readily explained by the noncomparability of initial lipoprotein levels in the two groups studied. Their experience emphasizes the importance of either using matched groups or proceeding with an internally controlled experiment.

Summary

Eleven of thirteen subjects with angina pectoris experienced moderate to marked relief after the intravenous injection twice weekly of 10 cc. of placebo solution consisting of 5 per cent glucose in water. The substitution of 100 mg. of heparin dissolved in 10 cc. of water for the glucose solution provided no advantage over the use of the placebo in alleviating heart pain.

About 100 days of parenteral treatment was required for most of these subjects to achieve maximal improvement.

This treatment had no persistent or cumulative effects on either the serum cholesterol or the serum S_f12-20 or S_f20-100 classes of lipoprotein.

The intravenous injection of 100 mg. of heparin in ambulatory patients twice weekly for periods up to 151 days and for a total of 1323 patient days was accompanied by no hemorrhagic disturbances or other untoward effects.

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References

1. Lerman, J., and White, P. D. Metabolic changes in young people with coronary heart disease. *J. Clin. Investigation* 28:914, 1946.
2. Underdahl, L. O., and Smith, H. L. Coronary artery disease in women under age of forty. *Proc. Staff Mem., Mayo Clin.* 22:679-682, 1947.
3. Adlersberg, D., Parets, A. D., and Boas, E. D. Genetics of atherosclerosis: studies of families with xanthoma and unselected patients with coronary artery disease under age of fifty years. *J. A. M. A.* 141:246-254, 1949.
4. Keys, A. Human atherosclerosis and diet. *Circulation* 5:115, 1952.
5. Steiner, A., and Domanski, B. Effect of "soya lecithin" on serum cholesterol level of man. *Proc. Soc. Exper. Biol. & Med.* 55:236-238, 1944.
6. Morrison, L. M., and Gonzalez, W. F. Results of treatment of coronary arteriosclerosis with choline. *Am. Heart J.* 39:729-736, 1950.
7. Gofman, J. W., et al. Role of lipids and lipoproteins in atherosclerosis. *Science* 111:166-171, 1950.
8. Graham, D. M., et al. Blood lipids and human atherosclerosis. II. Influence of heparin upon lipoprotein metabolism. *Circulation* 4: 666, 1951.
9. Chandler, H. L., Lawry, E. Y., Potee, K. G., and Mann, G. V. Spontaneous and induced variations in serum lipoproteins. *Circulation* 8:723-731, 1953.
10. Engelberg, H. Heparin therapy of severe coronary atherosclerosis, with observations of its effect on angina pectoris, two-step electrocardiogram, and ballistocardiogram. *Am. J. M. Sc.* 224:487-495, 1952.
11. Russek, H. I., Urbach, K. F., and Doerner, A. A. Effect of heparin in cases of coronary insufficiency; evaluation by electrocardiographic tests. *J. A. M. A.* 149:1008-1010, 1952.
12. Miller, H., Zinn, W. J., and Griffith, G. C. Effect of heparin and placebo therapy in coronary artery disease. *Circulation* 6:679, 1952.
13. Binder, M. J., Kalmanson, G. M., Drenick, E. J., and Rosove, L. Clinical evaluation of heparin in treatment of angina pectoris. *J. A. M. A.* 151:967-970, 1953.

14. Grüner, A., Hilden, T., Rasschou, F., and Vogelius, H. Heparin treatment of angina pectoris. *Am. J. Med.* 14:633-637, 1953.

15. Rinzler, S. H., et al. Effect of heparin in effort angina. *Am. J. Med.* 14:438-447, 1953.

16. Master, A. M., Nuzi, S., Brown, R. C., and Parker, R. C., Jr. Electrocardiogram and "two-step" exercise: test of cardiac function and coronary insufficiency. *Am. M. J. Sc.* 207:435-450, 1944.

17. Gruner, T., et al. Method for evaluation of effects of drugs on cardiac pain in patients with angina of effort: study of khellin (visnamin). *Am. J. Med.* 9:143-155, 1952.

18. Abell, L. L., Levy, B. B., Brodie, B. B., and Kendall, F. E. Simplified method for estimation of total cholesterol in serum and demonstration of its specificity. *J. Biol. Chem.* 195:357-366, 1952.

19. Lee, R. I., and White, P. D. Clinical study of coagulation time of blood. *Am. J. M. Sc.* 145:495-503, 1913.

EFFECTS OF ISONIAZID ON PATIENTS WITH TUBERCULOSIS AND MENTAL ILLNESS

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AFTER the favorable early reports[1, 2] on the use of isonicotinic acid hydrazide (isoniazid) for the treatment of tuberculosis, therapy with this drug was begun for a group of psychotic patients in the tuberculosis isolation building of the Boston State Hospital. In earlier descriptions of the mood change of patients incident to isoniazid therapy, "a subtle, general stimulation" of the mood was noted.[2] One could not tell, however, from the initial investigations, whether the "stimulating" effect was secondary to reduction in patients' toxicity or whether isoniazid, in itself, had a euphoric action. The question was therefore raised whether some of the helpful effects of the new drug were due to elation of mood or whether mood changes were the result of physical recovery.

More recent reports[3] also fail to be specific about these points although the impression is gained that diminution in toxicity antedates the return of a sense of well-being. Selikoff, Robitzek and Ornstein[3] make the following observation:

> Appetite begins to improve, especially when it has been poor, as early as the second day of therapy, and improvement is almost always noted by the end of the first week. At this time, return of strength, energy, and sense of well-being begins to become manifest, and improvement is marked by the end of three weeks. This reversal of systemic toxicity is more marked in toxic cases, and may be seen even in moribund patients.

In another survey, dealing with 390 patients and set up by the directors of 22 tuberculosis hospitals, co-ordinated through a central office in the United States Public Health Service, the effects of isoniazid were determined in a controlled experiment in which random selection of patients was assured.[4] It was concluded that "isoniazid appears, at the least, an extremely effective antituberculous agent for short-term therapy." No note was made, however, in this extensive report, on the effect on patients' moods.

One study[5] deals specifically with the effects of isoniazid in the tuberculous insane. In this report, 48 patients were carried through a course of isoniazid therapy for ninety days; some degree of appetite improvement was seen in more than two thirds of the patients treated. Although patients were selected for study on the basis of their tuberculosis and not on that of their psychosis, some degree of change in mental behavior was noted in 21 of the 48 patients studied, being marked in 6, moderate in 12 and slight in 3. Twenty-seven patients failed to show any degree of mental improvement.

Since improvement had not been anticipated when the investigation was begun, suitable controls were not included in the study. The authors, however, regarded the improvement as more than a temporary feeling of euphoria or increased sense of well-being and as actually representing a renewed contact with reality in some patients who had been withdrawn and hallucinative for a long time. Many patients showing no change in mental behavior were only mildly psychotic and displayed no gross evidence of psychosis. The authors add:

> We should like to call attention at this time to the fact that the greatest degree of improvement occurred, as a general rule, among patients with a diagnosis of schizophrenia, without any significant relation to the type. Since it is not our purpose here to assume the role of the psychiatrist but rather to point out that we have observed a change in mental behavior which we feel is directly related to the administration of isonicotinic acid hydrazide, individual case reports have not been included. We are simply reporting these changes in the hope that we may stimulate an interest in further research into this interesting phenomenon.

In May, 1952, shortly after the appearance of reports on the use of isoniazid, this drug was included in the general therapeutic program of the tuberculosis unit so that during the period covered by the present report (May, 1952, through March, 1953) 78 patients received this agent; the results are considered below. Since the diagnosis of tuberculosis was made by x-ray findings in 17 patients, who were started on isoniazid before or without the finding of acid-fast bacilli, they are not evaluated for change in pulmonary status but are included in the evaluation of change in mental status.

Eventually, isoniazid‡ became the first treatment in all newly discovered cases of pulmonary tuberculosis as well as in tuberculous patients who had not responded favorably to other agents. It replaced streptomycin in 7 cases in which that antibiotic had failed to produce improvement —

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‡Kindly supplied by Hoffmann-La Roche, Incorporated, Nutley, New Jersey, under the trade name, "Rimifon."

with improvement subsequently noted in 6. In 21 cases streptomycin was combined with isoniazid, when initial improvement with isoniazid was not sustained. Four patients who were receiving streptomycin were also given PAS.

The dosage of isoniazid approximated 4 mg. per kilogram of body weight. For convenience of administration, the dosage was standardized at 100 mg., three times a day, after meals. In 9 cases this dosage was increased to 200 mg., three times a day, after reports of increased benefit with larger doses. The dosage of streptomycin, when it was used in conjunction with isoniazid, was 1 gm. twice a week. For 3 patients operated on during this period streptomycin dosage was increased to 2 gm. a day for two weeks after operation. The dosage of PAS (used in 4 cases only) was 12 gm. daily in four divided doses.

In addition to these drugs, medical or surgical treatment was continued or instituted for each individual case, as was specific or nonspecific psychiatric therapy.

The duration of treatment for individual patients during the period reported on ranged from ten to three hundred days, with an average of one hundred and sixteen days. Except for 2 terminal cases, in which the patients died ten days after isoniazid was begun, the shortest period of treatment was thirty days.

Of the 78 patients, 58 were men, and 20 women. White patients numbered 74, Negro 3, and Chinese 1. The age range was twenty-one to eighty-four years, with an average age of forty-eight years.

Duration of pulmonary disease (as determined by date of discovery) before therapy with isoniazid varied from two days to twenty-five years, the former in a patient whose chest film and physical examination on admission constituted discovery. The average duration was four and one tenth years.

Duration of hospitalization for mental illness, as determined from date of this present admission to the hospital to the end of the period reported, varied from two days to thirty years, the average being nine years. The mental diagnoses of these patients are presented in Table 1.

The criterion for selection of patients for therapy was x-ray appearance suggestive of active pulmonary tuberculosis. Positive sputums were obtained on 59 of these 78 patients. Of the other 19 patients, 2 had extrapulmonary tuberculosis, and treatment with isoniazid was started on the remaining 17 without positive sputums because of former in a patient whose chest film and physical examination on admission constituted discovery. The average duration was four and one tenth years.

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The remaining 6 of the group without positive sputums are included, although they may not have had active tuberculosis, because this report covers changes in mental condition consequent to isoniazid therapy, as well as changes in tuberculous disease. The 17 patients who did not have positive bacteriologic findings are not included for discussion under changes in tuberculosis but are only under consideration for possible changes in mental status.

Of the 59 cases of active pulmonary tuberculosis, 1 was minimal, 25 moderately advanced, and 34 far advanced. In the 2 extrapulmonary cases, 1 patient had tuberculous proctitis, and the other had tuberculous spondylitis and nephritis. Four patients were moribund, with extensive disease, when isoniazid therapy was begun.

TABLE 1. *Mental Change in Patients on Isoniazid Therapy.*

Diagnosis	No. of Patients	Improvement	Remission	Deaths
		no. of cases	no. of cases	no. of cases
Schizophrenic reaction:				
Paranoid type	6	0	0	0
Catatonic type	10	0	0	1
Hebephrenic type	11	0	0	0
Simple type	4	0	0	0
Chronic, undifferentiated type	10	0	0	0
Paranoid state	6	0	0	0
Affective reaction	1	0	0	0
Mental deficiency (psychotic reaction)	2	0	0	0
Chronic brain syndrome:				
Associated with mongolism (mental deficiency)	1	0	0	0
Associated with cerebral arteriosclerosis	2	0	0	0
Associated with circulatory disturbance (congestive heart failure)	2	0	0	0
Associated with senile brain disease	2	0	0	0
Associated with alcohol intoxication (Korsakow's psychosis)	10	6	0	1
Acute brain syndrome associated with systemic infection (pulmonary tuberculosis)	6	1	4	1
Involutional psychotic reaction	1	0	0	0
Sociopathic personality disturbance (with psychotic reaction)	3	0	0	1
Without psychosis (recovered from postoperative schizophrenic reaction)	1	0	0	0
Totals	78	7	4	4

Two patients were diabetic, requiring 20 and 50 units of NPH insulin respectively. One patient with arteriosclerotic heart disease with cardiomegaly and 2 with hepatic cirrhosis with ascites required treatment for these conditions as well as for their pulmonary tuberculosis.

The treatment and progress were evaluated on the basis of the following criteria: roentgenographic changes, appetite, weight, temperature, bacteriology, mental status and side reactions.

Results of Therapy

Roentgenographic Changes

Favorable x-ray changes were noted in 42 of 57 patients, or 73 per cent. Two of the 59 patients with pulmonary tuberculosis had thoracoplasty, and a third, who had thoracoplasty, had clearing of the contralateral lung. The favorable change ranged from cavity closure, which was noted in 9 patients, to clearing of infiltrates, and decrease in cavity size. Nine patients showed no change, and in 6 cases x-ray examination revealed progressive worsening.

Appetite

Change in appetite was not easy to evaluate, but certain general observations could be made. In the first place, almost all patients who were toxic, with temperature elevations over 100°F., improved remarkably in appetite. This was true even of 3 moribund patients who died in spite of treatment. The very toxic patients, in some cases, showed appetites that could be called "ravenous." They consumed two or three helpings at each meal shortly after the start of treatment. As temperatures went down and signs of toxicity disappeared, their appetites became more normal, and they continued to eat well, but not ravenously.

These observations were complicated by the fact that some patients demonstrated fluctuation in their desire to eat for reasons that were obviously emotional rather than due to anorexia because of tuberculosis. For example, a patient with cavity closure and conversion of bacteriology by gastric culture continues to have a poor appetite, on occasion refuses to eat or eats only scraps from other patients' trays. Another severely withdrawn catatonic patient has shown x-ray clearing but must be spoon fed.

Weight

Change in weight was consistent with x-ray clearing. Of 49 patients who could be followed with weight records, 40, or 81 per cent, gained weight. Three patients remained the same, and 6 patients lost weight. Twelve patients could not be followed with weight records, being either too moribund or unable to be weighedfor other reasons.

Temperature

Significant afternoon temperature elevation (99.6°F. or higher) was noted in 16 patients at the start of treatment. Reduction in temperature elevation was noted in 12 of these. Four moribund patients who died showed initially a drop in temperature, but temperatures again rose.

Bacteriology

Of the 59 patients with positive bacteriologic findings — that is, either positive sputum by direct smear or culture or positive gastric by direct smear and culture — not all could be re-evaluated during the time of this report. Only 18 were consistently followed so that a sputum or gastric was taken some time before the end of the period reported. Of this number, 12 showed conversion. Of the 2 patients with extrapulmonary tuberculosis, 1 with nephritis showed a conversion in urine cultures; the other left the hospital, his psychosis having undergone remission, to be continued in treatment for his tuberculous proctitis at another hospital (remission of the psychosis had begun before isoniazid was started).

Each of the cases of conversion in bacteriology showed x-ray changes consistent with arrested tuberculosis.

Mental Status

Evaluation of mental status was made on the basis of general appearance and behavior, stream of talk, mood, mental content, intellectual functions, orientation, apperception, insight and judgment. All 78 patients who were given isoniazid received this evaluation. Changes in mental status were noted in 11 patients while they were on isoniazid therapy.

Four patients with the diagnosis of acute brain syndrome associated with tuberculosis, schizophrenic reaction, showed a remission of the psychosis while on medication with isoniazid.

The following case reports are representative of these 4:

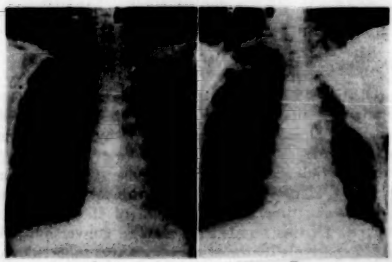
G. T., a 37-year-old married woman, was admitted to the Boston State Hospital on March 23, 1952. She was said to have become suddenly excited, violent and depressed; for 48 hours she had been crying and screaming. The patient had 5 children, with a normal delivery of the 5th 3 weeks before admission. No previous history of tuberculosis was given.

On admission she was confused, overactive and disturbed; at times she cried, and at others she burst into inappropriate laughter. On the ward she was unco-operative and destructive, tearing her clothes off and her bedding. This disturbed behavior continued for the 1st 4 months. She slept only with sedation.

The temperature was elevated on admission and fluctuated from 100 to 102°F. for the next 4 months. X-ray study showed soft infiltration throughout the left-upper-lung field and a large 5-cm. cavity at the level of the 1st rib (Fig. 1*A*).

The patient was placed on streptomycin for 3 months, without significant change. Attempt at left pneumothorax was unsuccessful. On isoniazid therapy, within 3 weeks the temperature subsided to normal levels, appetite improved, and she became quiet, co-operative with personnel and pleasant, but still slightly de-

pressed. The depression lifted completely in 2 more weeks, and for the rest of her hospital course she showed quite appropriate affect and was co-operative for all further procedures. Her behavior, which had been destructive and denudative, changed so that the was a very neatly dressed, pleasant woman. Her



A B

FIGURE 1. *Roentgenograms in G. T., Showing Infiltration and Cavity Formation* (A) *and Appearance after Isoniazid Therapy, Lobectomy and Thoracoplasty* (B).

stream of talk, which had been incoherent and flighty, became a modest, pleasant, inquiring manner of speaking.

Subsequently the left upper lobe was excised and a thoracoplasty performed since she had a tension cavity that did not close. Streptomycin and PAS, as well as penicillin, were added to the isoniazid medication for these operative procedures. She was released from the hospital 4 weeks after the 2d operation and 1 year after admission. Two gastric cultures were negative after operation; this case was classified as pulmonary tuberculosis, arrested. The operative procedures showed a good result (Fig. 1*B*).

M. G., a 30-year-old Negress, a clerical worker, married but without children, was discovered to have tuberculosis in October, 1951, and was admitted to a sanatorium, where she became so withdrawn and despondent, refusing to eat or talk and suffer-

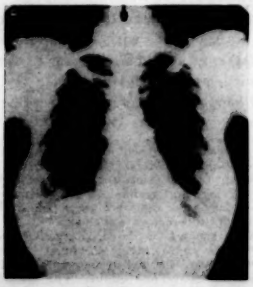


FIGURE 2. *Roentgenogram in M. G. after Two Months of Isoniazid Therapy.*

ing from hallucinations, that she was committed to Boston State Hospital after 1 week. She was placed on streptomycin, and pneumoperitoneum was induced, but she was resistive, negativistic and even destructive of equipment to such an extent that this procedure was discontinued. She was not responding to streptomycin, and her prognosis seemed extremely poor. She had a 5-cm. cavity in the left upper lobe, with infiltration at the base and spread to the right-middle-lung field. In her 18th month in the hospital she was placed on isoniazid therapy, streptomycin being discontinued. One month after isoniazid therapy had been started her behavior showed marked improvement. She became talkative and co-operative. Her depression lifted and she wanted to know why she was being kept in the hospital. At the same time, her appetite improved, and she gained 20 pounds in 2 months. In the same 2 months, x-ray evidence of the large cavity in the left upper lobe disappeared completely, and there was clearing in both lung fields, only small linear densities remaining (Fig. 2). She remained in the hospital for 2 more months, during which, although her psychosis was in remission, she was a management problem. She insisted she was being wrongly detained, refused to believe that she had been severely ill, mentally and physically, and demanded that she be released immediately. Finally, she was released to her husband for a trial visit at home, with instructions to continue isoniazid. Culture of gastric content on release from the hospital was negative for the tubercle bacillus. She returned to the hospital during the ensuing 6 months for follow-up care. She went back to work after being out for 2 months. The x-ray film shows no exacerbations, and there has been no return of clinical symptoms. She has been co-operative about outpatient visits, and her rapport with her psychiatrist became much better after she left the hospital. After seeing her x-ray films she no longer regarded her hospitalization as an incarceration.

These cases were diagnosed as acute brain syndrome associated with systemic infection (pulmonary tuberculosis). Seven cases in the series were similarly diagnosed. Except the 1 fatal case, all patients improved mentally. On the other hand, there were 41 patients with schizophrenic reaction who had shown this regressive pattern long before signs of pulmonary tuberculosis appeared; they continued to be schizophrenic.

The following case of chronic schizophrenia (incidentally, the least chronic, since the duration of the schizophrenia based on the time of hospitalization was the shortest of the 41 similar patients) did not show improvement while on isoniazid in contrast to the 2 cases presented above.

H. L., a 38-year-old married woman, was admitted to Boston State Hospital from another psychiatric hospital when her admission chest film showed densities suggestive of active pulmonary tuberculosis. The diagnosis was schizophrenic reaction — catatonic type. She had had 4 episodes of catatonic withdrawal in the past 3 years. At home, she had stopped doing her housework, stopped talking and refused to eat. One electric-convulsive treatment at the first hospital resulted in her beginning to eat again. On admission to Boston State Hospital gastric culture was positive. X-ray examination showed nodular densities in the left-upper-lung field, and the pulmonary tuberculosis was classified as minimal. Streptomycin was started and continued for 7 months. Then for 4 months, the patient received isoniazid alone. X-ray examination showed gradual clearing during the 11-month period; gastric cultures became negative, and at the end of this period she was released on a trial visit at home as a case of arrested tuberculosis. Although she was somewhat more talkative and outgoing than on admission she was still actively schizophrenic.

This patient showed no essential mental improvement on medication with isoniazid. Her depression had lifted while she was receiving streptomycin, but prescription of isoniazid did not improve her mental status, although the x-ray films continued to show clearing. She reached a plateau before starting isoniazid and improved no further. The course on isoniazid therapy was very much the

same as that of the other patients with chronic schizophrenia who were on it: there was no real change in the essential psychotic process.

The 2 patients previously discussed (G. T. and M. G.) demonstrated a change and a clear-cut remission of psychosis, corresponding with the improvement in the tuberculosis and alleviation of marked systemic toxicity. On the other hand, their psychoses were apparently precipitated by their tuberculosis, whereas in H. L. there was a long history of schizophrenia of at least three years' duration before the x-ray findings.

Another case of 1 of the 41 chronic schizophrenic patients in this series illustrates the improvement of a far-advanced case of pulmonary tuberculosis on isoniazid alone, with no essential improvement in the psychotic process.

G. L., a 24-year-old man, was admitted to Boston State Hospital in 1936. He presented a picture of a schizophrenic reaction, catatonic type. He was discovered to have pulmonary tuberculosis in 1949 by x-ray examination. His sputum was positive by direct smear. He received streptomycin and pneumoperitoneum, without improvement. Isoniazid was started in May, 1952, and continued without other medication during the 10 months of the survey. He gained weight, and gastric culture was negative for acid-fast bacilli after 10 months. In addition, he showed x-ray clearing of multiple cavities that had been evident at the beginning of isoniazid therapy (Fig. 3*A* and *B*). At the end of the survey period, the tuberculosis was considered arrested, but his disordered, bizarre, withdrawn behavior continued in spite of a concurrent series of 18 electric-shock treatments instituted in the hope of improving the impulsively assaultive behavior.

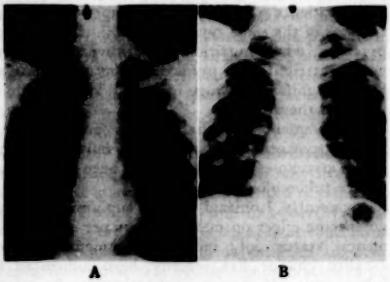


FIGURE 3. *Roentgenogram in G. L. before* (A) *and after Isoniazid Therapy* (B).

There was 1 patient (J. M.) with chronic schizophrenia who showed mental improvement on isoniazid while deteriorating physically. On isoniazid and streptomycin, he became bed ridden in spite of treatment. When he was bed ridden, with temperatures ranging from 101 to 102°F., he became quite talkative instead of being mute and withdrawn. One might conjecture that the mental change was due to toxicity in addition to the extra attention given him as a bed patient, rather than to the drugs he was receiving.

A patient who also had mental changes that did not fit into the pattern of improvement observed in the first 2 cases was admitted to Boston State Hospital for psychosis developing after a colostomy for tuberculous proctitis (he was in a remission of schizophrenic paranoid reaction before being started on isoniazid). He had been on isoniazid before he became psychotic, and until his remission no further isoniazid or streptomycin had been given, on the assumption that these drugs might have caused his psychosis. He was then placed on isoniazid again. During a two-month period of isoniazid therapy there was no return of his paranoid ideas, and he was returned for continued treatment to the hospital from which he had been referred.

Six patients in addition to those mentioned above showed mental changes, and these cases may be grouped together since the changes were similar and all were diagnosed chronic brain syndrome associated with alcoholic intoxication (Korsakow's psychosis). In all, there were 11 cases of alcoholic psychosis of the Korsakow type in the series. All showed slight to severe memory deficit, with complete inability to recall recent events and bizarre confabulations. Six of these 11 patients were originally very confused on admission, were started on isoniazid on admission and, along with improvement in tuberculosis, improved mentally during the course of treatment. This improvement consisted in lessening of confusion and lifting of apathy so that they became much more alert. All continue to show mild to severe memory deficit.

The improvement in mental status in these patients was not different from that seen in this type of psychosis when nutrition is improved. In fact, the 5 patients who did not show further improvement on isoniazid therapy had some weight gain and mental clearing that were due to good nutrition even before the isoniazid medication was begun. In all cases the x-ray films showed improvement, except for a patient who died of massive subcutaneous emphysema.

Another group of five patients received electroconvulsive therapy. Of these, 4 received five to twenty-five convulsive treatments; none of them showed any notable change. A fifth patient, who was started on isoniazid therapy on admission to the hospital, became a feeding problem a few days later. Frightened and withdrawn, as well as suddenly mute, he hid under his bed most of the day. An an emergency measure, one convulsive treatment resulted in his beginning to eat and talk again. Yet his mental status, as it appeared on admission, did not change essentially, and his psychosis could not be considered improved although the change mentioned appeared on isoniazid therapy. Significant changes in mental status are noted in Table 1.

Side Reactions

Most of the patients in this series were not communicative at all. All, in fact, being psychotic, had some aberrancy from what would be considered the normal in their communication with other people. Even those who talked were less communicative than might have been expected. Therefore, there were many who would not have mentioned subjective side effects even if they had been present.

There were no objective side effects during or after isoniazid medication.

Two patients who were talkative had subjective complaints. One complained of constipation, dizziness and headaches when her withdrawn, mute, catatonic behavior changed. She continued to complain of these effects in the hospital, but when last seen as an outpatient, she did not mention these complaints, although she was still receiving isoniazid.

Another patient complained of headaches and a rash on her forearms. (The rash was purely subjective; there were no visible signs of it.) She is being seen as an outpatient, having left the hospital, continues on isoniazid, and on her last visit she did not mention these complaints.

Mortality

Four deaths occurred during isoniazid therapy in cases that had been considered terminal at the start of treatment. One patient, a fifty-five-year-old woman, was severely depressed, with far-advanced pulmonary tuberculosis, Laënnec's cirrhosis and ascites. She died after twenty days on isoniazid therapy; the diagnoses were confirmed at autopsy. Another patient, a sixty-year-old man, had been treated for four years for pulmonary tuberculosis, receiving streptomycin and pneumoperitoneum unsuccessfully. Very moribund, he was started on isoniazid therapy. During the thirty subsequent days he showed an initial response, with increase in appetite and energy and lowering of fever, and then quickly failed. The third, a forty-year-old man, had pulmonary tuberculosis of twenty-five years' duration (orchiectomy for tuberculous orchitis had been performed twenty-five years previously), with periods of apparent arrest, and had been hospitalized for a chronic schizophrenic reaction, catatonic type, for fifteen years; he was moribund when isoniazid was begun and died fifteen days later.

A fourth patient, a fifty-one-year-old-man, died of subcutaneous and mediastinal emphysema after ten days of isoniazid therapy. He had been admitted to the hospital, four months before isoniazid was started, with far-advanced pulmonary tuberculosis and an alcoholic psychosis of the Korsakow type. Previously he had received streptomycin without improvement. His emphysema, a complication of pneumoperitoneum, began to develop two weeks before isoniazid treatment was begun. The diagnoses were confirmed at autopsy.

Summary and Conclusions

The observed effects of isoniazid on the tuberculosis process were not unlike those reported elsewhere as far as roentgenographic changes, appetite, weight, temperature, bacteriology and side effects are concerned. In some cases, isoniazid arrested the disease when streptomycin and collapse therapy had failed. In 21 cases in which initial improvement with isoniazid was not sustained, streptomycin was added to the program, with no clinical sign of drug resistance under the combined regimen.

Four patients with the diagnosis of acute brain syndrome associated with pulmonary tuberculosis showed remission of psychosis and also a slight improvement of the tuberculosis. Two patients improved slightly, without complete remission or arrest of pulmonary tuberculosis. In all these cases the psychosis developed after the pulmonary tuberculosis was discovered. In the patients who improved the psychosis was of comparatively short duration, apparently having been precipitated or aggravated by the pulmonary disease.

Of the other diagnostic categories, only the alcoholic patients showed mental improvement, and this was of the same type observed in the Korsakow psychosis when nutrition is improved, and could not be attributed to isoniazid. The other patients had no significant change in mental status while on isoniazid therapy.

Improvement in beha ior and personality, to the prepsychotic level, was noted only in patients whose psychoses seemed to have been precipitated by the tuberculosis process.

Apparently, isoniazid is not a euphoriant and has no specific effect on mental status per se, affecting mental status only indirectly if mental or personality change has already been influenced by tuberculosis. If change or deterioration in mental status is attributed to toxic effects of tuberculosis, treatment with isoniazid can be expected to result in improvement in mental status paralleling the improvement of tuberculosis.

We are indebted to Mrs. Lillian O'Laughlin, R.N., and Mrs. Eugenia Green, for their assistance in the care of the patients.

References

1. Bernstein, J., Lott, W. A., Steinberg, B. A., and Yale, H. L. Chemotherapy of experimental tuberculosis. V. Isonicotinic acid hydrazide (sydranid) and related compounds. *Am. Rev. Tuberc.* 68:357-364, 1952.
2. Selikoff, I. J., and Robitzek, E. H. Tuberculosis chemotherapy with hydrazine derivatives of isonicotinic acid. *Dis. of Chest* 21:385-438, 1952.
3. Selikoff, I. J., Robitzek, E. H., and Ornstein, G. G. Treatment of pulmonary tuberculosis with hydrazide derivatives of isonicotinic acid. *J. A. M. A.* 150:973-980, 1952.
4. Mount, F. W., and Ferebee, S. A. Control study of comparative efficacy of isoniazid, streptomycin-isoniazid, and streptomycin-para-aminosalicylic acid in pulmonary tuberculosis therapy. II. Report on twenty-week observations on 390 patients with streptomycin-susceptible infections. *Am. Rev. Tuberc.* 67:108-113, 1953.
5. Krieger, A. E., Sanderson, A. G., Vik, M., and Myers, J. A. Effects of isonicotinic acid hydrazide in mentally ill patients. *Dis. of Chest* 23:28-35, 1953.

THE MECHANISM OF SYNCOPE ASSOCIATED WITH CHRONIC AURICULAR FIBRILLATION WITHOUT EVIDENCE OF ORGANIC HEART DISEASE*

Cure, after Ten Years, by Restoration of Sinus Rhythm with Quinidine

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THE unusual opportunity of observing a patient with longstanding auricular fibrillation during an episode of syncope and of studying the possible mechanism responsible for the syncopal attack impels us to report the following case. Syncope or faintness is not unusual in patients with *paroxysmal* auricular fibrillation at the onset of the arrhythmia due to tachycardia or the sudden change in rhythm.[1-4] However, it is not a part of the clinical picture of established auricular fibrillation with relatively slow and unchanged ventricular rate in the patient with organic heart disease. Although syncope is often listed as one of the possible symptoms of chronic auricular fibrillation without evidence of organic heart disease,[5, 6] we have been unable to find any published record of observations made during the period of syncope that might explain its mechanism or of any electrocardiograms taken during the attack. We were able to observe one patient during a period of syncope sufficiently protracted to permit clinical and electrocardiographic studies.

The association of syncopal attacks with the arrhythmia presented not only the problem of mechanism but also that of the proper therapeutic management. Chronic auricular fibrillation is generally regarded as a serious and usually irreversible arrhythmia associated with advanced organic heart disease.[7] Except in cases due to hyperthyroidism, treatment is ordinarily directed against concomitant congestive heart failure or is designed to slow a rapid ventricular rate by the administration of digitalis. In more recent years there has been an increasing trend toward attempting to restore a regular sinus rhythm by means of quinidine, even in the presence of heart failure and embolization.[8, 9] The following case serves as a reminder that chronic auricular fibrillation does not always denote underlying advanced heart disease and that this arrhythmia may occur in the absence of any apparent cardiac or other organic heart disease.[5, 6, 9, 10, 11] It also demonstrates that regular sinus rhythm may be restored even after auricular fibrillation has persisted for many years.

CASE REPORT

A 35-year-old film producer had been told in 1942, when he was 26, that he had auricular fibrillation. He considered himself in good health at the time. In 1949, after a severe emotional strain, he had an attack of palpitation, which was controlled by sedation; since then he has been aware of palpitation after strenuous exertion or after a large meal. He experienced episodes of faintness and severe weakness on several occasions unrelated to any unusual activity or strain. Previous examinations had always revealed a heart of normal size and without cardiac murmurs. The basal metabolic rate in 1942 was −16 per cent. He had had no dyspnea, orthopnea, angina pectoris or edema. There was no history of rheumatic fever or diphtheria.

In March, 1950, he was treated at his home by one of us for acute maxillary sinusitis and viral pneumonia, which responded to penicillin and oxytetracycline therapy. During this illness auricular fibrillation was noted again, but no cardiac murmurs were detected, and the heart size was normal by fluoroscopy and radiography. The blood pressure was 120/70. At no time had he received digitalis or quinidine, nor had he been taking any medication immediately before the episode described below.

At 9 a.m. on March 12, 1951, he experienced a series of syncopal reactions, which became protracted and required hospitalization later that day. On the previous evening he had worked to a late hour and had been under more than usual strain. While descending in an elevator the next morning, he had 2 episodes of sudden severe weakness and faintness, breathlessness and palpitation. When brought to his physician's office, he was unable to sit up or stand. Syncope recurred when he tried to get up from the examining table, and he had to be hospitalized.

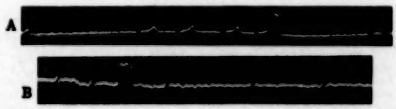

FIGURE 1. *Electrocardiogram Taken during the Initial Attack of Syncope.*

A = *Lead 1, with the patient in the recumbent position, showing auricular fibrillation with periods of ventricular asystole for 2 seconds and 2.2 seconds.*

B = *Lead 3, after intravenous administration of 0.8 mg. of atropine. Periods of ventricular asystole are slightly shortened.*

Physical examination revealed a tall, asthenic but well developed man who appeared acutely ill and manifested marked diaphoresis, cold clammy skin and great pallor. The heart rate was totally irregular, and the apical and radial pulses were 80 per minute, without a pulse deficit. The pulse volume was small. The blood pressure in the recumbent position was 85/54. When he sat up, the blood pressure fell rapidly, the pulse became weaker and finally imperceptible, and syncope recurred. He was given 3 minims of epinephrine by hypodermic as well as 60 mg. of phenobarbital and 20 mg. of Paredrine Hydrobromide by mouth. For 3 hours his condition was unchanged, and the blood pressure in the recumbent position remained between 80 and 90 systolic, falling precipitously when he tried to rise.

The heart appeared to be of normal size according to percussion and palpation of the apical impulse. The heart sounds were of normal quality. The cardiac rhythm was totally irregular, and there was an occasional long pause. Electrocardiograms taken during the initial syncopal attacks before admission showed auricular fibrillation, with periods of ventricular asystole of 2 seconds' duration (Fig. 1*A*). A tracing taken ½ hour after the intravenous administration of 0.8 mg. of atropine demonstrated a slight reduction in the duration of the periods of asystole (Fig. 1*B*). Carotid-sinus stimulation on both sides of the neck did not perceptibly alter the cardiac rate.

Examination of the blood revealed a hemoglobin of 13.5 gm. per 100 cc. and a white-cell count of 5300, with 70 per cent seg-

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mented neutrophils and 30 per cent lymphocytes. The urine had a specific gravity of 1.018 and was negative for albumin and sugar; the sediment was normal. The stools were negative for occult blood. The erythrocyte sedimentation rate was 4 mm. per hour (Westergren method). The fasting blood sugar was 80 mg., and the serum cholesterol 320 mg. per 100 cc., and the plasma potassium 5.1 milliequiv. per liter. Radioiodine excretion after a tracer dose of I^{131} was 59 per cent (normal).

The findings on physical, electrocardiographic, x-ray and laboratory examinations were interpreted as excluding organic cardiac disease, hyperthyroidism, Addison's disease or any organic disease that might be responsible for syncope.

The patient was given 20 mg. of Paredrine Hydrobromide by mouth 3 times daily. The blood pressure on the 2d hospital day rose to 102/60. He recovered gradually and felt fairly well after an additional 24 hours. It was then decided to attempt to establish regular sinus rhythm. Accordingly, he received orally 0.4 gm. of quinidine sulfate every 2 hours for 5 doses. No effect on the cardiac rhythm was observed on the 1st day, although the pulse rate increased moderately. There was mild diarrhea, which was not disabling. On the next day he received 0.6 gm. of quinidine sulfate every 2 hours for 5 doses. After the 2d dose of quinidine on the 2d day of treatment (after a total of 3.2 gm. of quinidine), the pulse became regular, and regular sinus rhythm was present, as demonstrated by electrocardiograms (Fig. 2).

FIGURE 2. *Electrocardiograms on the Second Day of Treatment. Sinus rhythm was established after 3.2 gm. of quinidine in twenty-four hours. Prominent, wide P waves are seen in Leads 2, 3, aVF and aVF. The R-R' pattern is apparent in Leads V_1 to V_3. The T waves are broad and notched in Leads V_1 to V_4 and associated with U waves. Intra-auricular and intraventricular conduction defects are probably due to quinidine. Electrocardiograms subsequently became normal.*

Examination of the heart then revealed a regular rate of 66 beats per minute and no accentuated sounds or murmurs. On the 3d day of quinidine therapy 0.2 gm. of quinidine 3 times a day was begun as a maintenance dose. The patient left the hospital on March 21, in good condition. He was examined 10 days later and found to be normal, and the cardiac rhythm was still regular despite the fact that he had discontinued quinidine. An electrocardiogram was normal, and the rate was 65 beats per minute. At the time of last examination, 18 months after reversion to regular rhythm, the pulse was entirely regular and normal; during the interval he had had no further attacks of excessive weakness or syncope. He has noted occasional extrasystoles after heavy smoking or extreme nervousness. He has experienced occasional dull pain in the left upper anterior aspect of the chest followed by eructation. He has otherwise been in excellent health and spirits and has engaged in normal physical activity.

DISCUSSION

The essential abnormalities that could be related to syncope in this case were the periods of cardiac standstill, the mild hypotension during recumbency and the extreme hypotension when the patient was upright. Syncope, occurring at the onset of paroxysmal auricular fibrillation, has been related to hyperactive vagal reflexes resulting in cardiac standstill.[4] However, in the case reported above, the episode of syncope could not be attributed to the cardiac standstill both because the duration of the periods of standstill — namely, two seconds or less — was too brief to cause syncope and because the occurrence of syncope did not coincide with the periods of cardiac standstill. Furthermore, definite faintness or syncope did not occur when the patient was recumbent, despite the hypotension, presumably because the hypotension was not sufficiently severe. Syncope must therefore be attributed to postural hypotension, since it occurred only when the patient tried to assume the upright position, the blood pressure rapidly falling to minimal values and the pulse becoming imperceptible. The immediate cause of the syncope was the cerebral ischemia resulting from the maximal fall in blood pressure.

Since fainting due to postural hypotension may occur independently of cardiac disease or cardiac arrhythmia,[13] it is possible that the syncope in this case was unrelated to the auricular fibrillation. Although this possibility cannot be absolutely excluded, there are several indications that the syncope and postural hypotension were at least in part caused by the cardiac arrhythmia. It has already been stated that syncope has been repeatedly mentioned as one of the symptoms in cases of chronic auricular fibrillation without organic heart disease, although the presence of postural hypotension as the immediate mechanism has not been noted. The frequency of syncope appears to exceed by far that to be anticipated on the basis of accidental association. A causal relation between auricular fibrillation and syncope in this patient is suggested by the recurrent episodes so long as the auricular fibrillation was present and their absence for two years after the arrhythmia was abolished.

There are insufficient data to determine the mechanism by which auricular fibrillation may predispose to postural hypotension and consequent syncope. The association of bradycardia and brief periods of asystole with the postural hypotension and syncope suggests that the syncope should be attributed to a vasodepressor mechanism of the kind observed with the common faint or, less probably, with a hypersensitive carotid sinus.[15, 16] The occurrence of sweating, pallor and nausea in this case is also characteristic of the vasodepressor type of syncope. That the vasodepressor syncope in this case was not due to carotid-sinus hypersensitivity is indicated by the inability to induce cardiac standstill or vasodepression by manipulation of the carotid sinus, either during auricular fibrillation or after sinus rhythm had been established. That the syncope occurred in the presence of auricular fibrillation and disappeared when the rhythm was normal suggests that the heart with auricular fibrillation in some way sensitizes the neural arc responsible for the vasodepressor type of syncope. There is no collateral evidence to support this possibility or to explain such a mechanism.

Psychologic factors are commonly held responsible for vasodepressor syncope in normal subjects with normal cardiac rhythm. Hyperventilation from

psychogenic disturbance may act as the trigger mechanism that evokes the vasodepressor response in some cases.[16] The possible role of psychologic disturbance was therefore considered in this case for its possible relation both to the vasodepressor syncope and to the chronic auricular fibrillation without underlying organic heart disease. There is a reasonable basis for psychologic factors in this case, not only because of the patient's basic neurotic pattern but also because the syncopal episodes were most likely to occur during periods of unusual emotional strain. On the other hand, these psychologic factors are considered not to have been the sole cause for the syncopal attacks, which did not recur after regular cardiac rhythm was restored in spite of the fact that the basic neurosis and the emotional strains were apparently unaltered. One might assume that the syncopal syndrome was exclusively due to psychologic factors if one presupposed that the only effect of the fibrillating heart was to induce anxiety. Restoration of sinus rhythm would then be regarded as having abolished the vasodepressor reflex by eliminating anxiety over the cardiac abnormality.

It should be emphasized that the observations here reported refer to one episode of syncope in one patient. It is therefore possible that some other mechanism was responsible for other attacks in this patient or in other patients. However, we have been unable to find any record of blood pressure, pulse rate and electrocardiographic studies during an attack of syncope in a patient with chronic auricular fibrillation without evidence of organic heart disease. The possibility of some other causative mechanism is only conjectural at present.

It was decided to attempt to restore sinus rhythm not only because of the evidence of greater effectiveness of the heart when its rhythm is regular than when it is experiencing auricular fibrillation,[16-18] and the greater risk of heart failure[6, 19] and embolization[20] in the latter state, but also because this patient was repeatedly disturbed by palpitation and by episodes of weakness or faintness, as well as by actual syncope. His cardiac irregularity had been the cause of his rejection from the armed forces and for life insurance. He had avoided sports, including swimming, and many moderate activities for fear of damage to his heart. The sinus rhythm has thus far persisted for two years since its restoration, without maintenance doses of quinidine. During this period there have been no episodes of weakness, faintness or syncope, which were the actual complaints that led the patient to seek medical care.

Summary

A case of persistent auricular fibrillation for ten years, without evidence of organic heart disease, in a patient who experienced episodes of weakness, faintness or syncope is reported.

Observations, including electrocardiograms, made during a prolonged attack of recurrent syncope offer the first reported basis for explaining the mechanism of fainting in a case of chronic auricular fibrillation. Although there were brief periods of cardiac standstill and hypotension was present during recumbency, the episodes of syncope were actually due to postural hypotension and not to the standstill. Syncope could not be induced by carotid-sinus pressure.

The attacks of syncope are attributed directly to a vasodepressor reflex, but the mechanism and the neural pathway are uncertain. A causal relation between the auricular fibrillation and the syncopal attack is suggested by the occurrence of the latter only while auricular fibrillation persisted, but not after sinus rhythm was established. The findings in this episode of syncope and the suggested mechanism may or may not apply to other attacks in the same patient or in other patients.

Despite the ten-year duration of the auricular fibrillation, sinus rhythm was established in twenty-four hours by a total of 3.2 gm. of quinidine and has now persisted for two years without maintenance doses of quinidine.

Restoration of sinus rhythm has been followed thus far by elimination of the attacks of faintness and syncope.

References

1. Parkinson, J., and Campbell, M. Paroxysmal auricular fibrillation: record of 200 patients. *Quart. J. Med.* 24:67-100, 1930.
2. Fowler, W. M., and Baldridge, C. W. Auricular fibrillation as only manifestation of heart disease. *Am. Heart J.* 6:183-191, 1930.
3. Levy, R. L. Paroxysmal auricular fibrillation and flutter without signs of organic cardiac disease in 2 brothers. *J. Mt. Sinai Hosp.* 8:765-770, 1942.
4. Comess, W. J. Mechanism for syncopal attacks associated with paroxysmal auricular fibrillation. *New Eng. J. Med.* 227:134-136, 1942.
5. Hanson, H. H., and Rutledge, D. I. Auricular fibrillation in normal hearts. *New Eng. J. Med.* 240:947-953, 1949.
6. Phillips, E., and Levine, S. A. Auricular fibrillation without other evidence of heart disease. *Am. J. Med.* 7:478, 1949.
7. Friedberg, C. K. *Diseases of the Heart.* 1081 pp. Philadelphia: Saunders, 1949. P. 277.
8. White, P. D., and Blumgart, H. L. Cessation of repeated pulmonary infarction and of congestive failure after termination of auricular fibrillation by quinidine therapy. *J. Mt. Sinai Hosp.* 8:1095-1103, 1942.
9. Askey, J. M. Quinidine in treatment of auricular fibrillation in association with congestive failure. *Ann. Int. Med.* 24:371-384, 1946.
10. Friedlander, R. D., and Levine, S. A. Auricular fibrillation and flutter without evidence of organic heart disease. *New Eng. J. Med.* 211:652-659, 1934.
11. Orgain, E. S., Wolff, L., and White, P. D. Uncomplicated auricular fibrillation and auricular flutter: frequent occurrence and good prognosis in patients without other evidence of cardiac disease. *Arch. Int. Med.* 57:493-513, 1936.
12. Engel, G. L. Mechanisms of fainting. *J. Mt. Sinai Hosp.* 12:170-190, 1. ill. *Fainting: Physiological and psychological considerations.* 140 pp. Springfield, Illinois: Charles C. Thomas, 1950.
13. Ferris, E. B., Jr., Capps, R. B., and Weiss, S. Carotid sinus syncope and its bearing on mechanism of unconscious state and convulsions: study of 32 additional cases. *Medicine* 14:377-456, 1935.
14. Engel, G. L., Romano, J., and McLin, T. R. Vasodepressor and carotid sinus syncope: clinical, electroencephalographic and electrocardiographic observations. *Arch. Int. Med.* 74:105-119, 1944.
15. Engel, G. L., Ferris, E. B., Jr., and Logue, M. Hypersyncopilation: analysis of clinical symptomatology. *Ann. Int. Med.* 27:683-704, 1947.
16. Hecht, H. H., Ochsner, W. J., and Samuels, A. J. Cardiovascular adjustments in subjects with organic heart disease before and after conversion of atrial fibrillation to normal sinus rhythm. *J. Clin. Investigation* 30:647, 1951.
17. Kory, R. C., and Meneely, G. R. Cardiac output in auricular fibrillation and observations on effects of conversion to normal sinus rhythm. *J. Clin. Investigation* 30:653, 1951.
18. Hanson, W. R., McCredie, R. L., and Kinsman, J. M. Auricular fibrillation: hemodynamic studies before and after conversion with quinidine. *Am. Heart J.* 44:499-516, 1952.
19. Brill, I. C. Auricular fibrillation with congestive failure and no other evidence of organic heart disease. *Am. Heart J.* 13:175-182, 1937.
20. Daley, R., Mattingly, T. W., Holt, C. L., Bland, E. F., and White, P. D. Systemic arterial embolism in rheumatic heart disease. *Am. Heart J.* 42:566-581, 1951.

SPONTANEOUS RUPTURE OF THE NORMAL ESOPHAGUS*

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WITHIN a month during the past spring we had the unusual experience at the Beverly Hospital of caring for 2 patients with spontaneous rupture of the esophagus. Although this condition is not a medical curiosity, it is infrequent, and as a result, the clinical picture is not widely recognized. If this accident is undiagnosed and untreated, the result is invariably fatal. There are few other surgical emergencies in which early diagnosis and prompt treatment are so necessary to save life. The chief cause of death is delay, and the cause of delay is that esophageal rupture is not suspected. Yet when classic, the clinical picture may be so clear that the diagnosis may be made over the telephone.

CASE REPORTS

CASE 1. P. O., a 69-year-old retired man, was admitted to the hospital on March 23, 1953, for treatment of a chronic duodenal ulcer, which was causing intractable pain and occasional hematemesis. Ten years previously he had been operated on for perforated duodenal ulcer. Three months earlier he was in the hospital with similar symptoms, and a gastrectomy was advised but refused.

On this admission he was nauseated, had some dull pain in the epigastrium but was in no acute distress. Examination was not remarkable, and a chest film shortly after admission was normal except for healed tuberculosis of the right apex.

Four hours later he vomited undigested food and then complained of pain in the upper abdomen, which radiated to the mid-back. He was pale and restless. The respirations were 28, and the pulse 76, and the blood pressure fell from 120/76 on admission to 80/50. Pain was relieved by 75 mg. of Demerol; he slept in naps and did not seem profoundly ill, although the blood pressure remained below 100 during the night. On the following morning one surgeon thought that he might have a perforated ulcer and obtained a plain abdominal film, which showed no free air under the diaphragm. Whereas the upper abdomen was moderately rigid and tender, the lower abdomen was soft. The rapid, "catching" type of respiration, with pain limiting each inspiration, was striking. The patient was not in collapse, nor was his pain very severe.

Coronary thrombosis, dissecting thoracic aneurysm, acute pancreatitis and incarcerated diaphragmatic hernia were considered. The urinary diastase was normal, and an electrocardiogram showed no recent myocardial infarction.

An internist considered a coronary thrombosis unlikely, believing that the pathologic process was below the diaphragm, whereas the surgeon thought that it was above. In this case the surgeon was correct by about 1 cm. (This point is mentioned to emphasize the fact that rupture of the esophagus should be considered when localization above or below the diaphragmatic meridian is under question.) Later, the internist detected dullness at the left base and heard an unusual, evanescent clicking sound. Because of these findings, another chest film was taken, which showed fluid at both bases. Review of this film later showed mediastinal emphysema. Thoracentesis on the left produced gastric fluid. Since it was not certain whether the stomach had been inadvertently entered, the right pleural cavity was aspirated, and the diagnosis was made when similar fluid was obtained. Twenty-four hours had elapsed since the onset of symptoms because the diagnosis of perforation of the esophagus had not been considered earlier.

Under endotracheal anesthesia thoracotomy was performed, about 400 cc. of gastric fluid being aspirated from the left pleural cavity. The surfaces of the lung, diaphragm and mediastinum were covered by a gray exudate. The mediastinal pleura was completely disintegrated, and one could pass a finger readily through the mediastinum into the right pleural cavity; 1 cm. above the diaphragm there was a tear, 3 cm. in length, in the left lateral wall of the esophagus. The adjacent esophagus was normal. The mucosa was inverted and the esophagus was sutured with 5 No. 000 silk Lembert sutures. The pleural cavity was drained with an underwater seal. The patient's condition at the end of the operation was much improved. Culture showed beta-hemolytic streptococcus, and adequate antibiotic therapy was administered.

On the day after operation, the nonprotein nitrogen was 170 mg. per 100 cc., gradually rising to 230 mg. per 100 cc. A hydrothorax developed on the right and was aspirated. On the 6th day methylene blue, administered by mouth, was recovered from the pleural drainage. The patient died on the 8th postoperative day. Autopsy disclosed complete dissolution of the suture line in the esophagus and extensive mediastinitis.

In the entrance rotunda of Vanderbilt Hall, Harvard Medical School, a saying of Pasteur is inscribed in French for the edification of the medical students: "In the fields of observation chance favors those minds which are prepared." The truth of this maxim is well illustrated by the following case.

CASE 2. J. H., a 69-year-old retired man, was admitted to the hospital because of weakness, loss of weight and hoarseness, with a diagnosis of carcinoma of the stomach. In 1918 a gastroenterostomy had been performed for a duodenal ulcer, and he had had no symptoms until the present illness, which had begun 10 months previously.

Thirty hours after admission he vomited, and severe epigastric pain radiating to the back on the left then developed. The upper abdomen was tender; a diagnosis of perforated ulcer was considered by his physician. A surgical consultant found tenderness in the epigastrium and some rigidity. In addition, he observed crepitation in the neck.

The patient had difficulty in taking a deep breath, but there was no intense distress and no collapse. The blood pressure had fallen from 108/60 on admission to 98/60. The pulse was 54, and the respirations 24. A swallow of barium confirmed the diagnosis.

Under endotracheal anesthesia operation was carried out 6 hours after the onset of the severe pain. Thoracotomy was performed on the left. Pleural adhesions had walled off a pocket containing about 400 cc. of thin, cloudy, green fluid. This communicated with a tear in the esophagus, 3 cm. in length, immediately above the diaphragm on the left lateral wall. The adjacent esophagus was normal. The laceration was closed with 2 layers of Lembert sutures of No. 000 silk. The pleural cavity was drained with an underwater seal. A jejunostomy was performed.

The postoperative course was uneventful. One month later abdominal exploration was performed for carcinoma of the stomach. Unfortunately, the disease was so extensive that nothing could be done. This patient left the hospital a week later and is still fairly comfortable.

ETIOLOGY

The term "spontaneous rupture" is inaccurate. The condition under discussion was a complete tear in the lower esophagus precipitated by vomiting that occurred in patients who presumably had a normal esophagus immediately before the accident. The term "spontaneous" is used to distinguish this entity from other perforations caused by external

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trauma, instrumentation, inlying tubes, missiles or perforation of ulcers. Although all are essentially traumatic, the evolution of the clinical picture is different in the latter. The same principles of early definitive repair apply to both groups.

It is well known that vomiting may cause injury to the esophagus. Vinson[1] reported cases of hyperemesis gravidarum in which mucosal rents developed that later healed, with stricture formation, and Weiss and Mallory[2] described mucosal lacerations just above the cardia in alcoholic patients caused by repeated retching and vomiting; these patients died of massive hematemesis. The authors were able to trace a sequence in 1 patient from a laceration to a chronic ulcer followed later by a complete rupture through the whole esophageal wall after vomiting. Although this rupture "in stages" may be the etiologic sequence in alcoholism, many patients with spontaneous rupture give no antecedent history of vomiting, hematemesis or alcoholism. It must be assumed that spontaneous rupture in most cases occurs through the whole esophageal wall with a single forceful insult to a previously normal esophagus.

Clinical Picture

The prompt recognition of this entity requires a knowledge of the physical events that follow the sudden rent in the lower esophagus, caused by forceful retching or vomiting, and an inclusion of this possibility in the differential diagnosis of problems of acute pain in the upper abdomen. In the classic picture, during or shortly after vomiting, the patient complains of severe pain in the upper abdomen and the anterior lower portion of the chest. Pain may be severe and may move to the back in the lower thoracic region and upward behind the sternum and into the shoulder; the pain is unremitting, causing breathing to be limited, and respirations may become short and rapid. The clinical signs of shock soon develop.

Within a few hours, the acid gastric juice digests the mediastinal pleura and spills over into one or both pleural cavities. The development of pleural effusions may be extensive and rapid. The patient observed a few hours after rupture is in acute distress. He is dyspneic, cyanotic and in peripheral vascular collapse. The upper abdominal wall may be rigid and tender, but the lower abdomen is soft. Because of the upper abdominal guarding and the rapid respirations, the surgeon is uncertain whether he is dealing with trouble above or below the diaphragm. When there is this clinical indecision whether the pathologic process is in the thorax or the abdomen, he should consider rupture of the esophagus as a possibility. Since the rupture usually occurs immediately above the diaphragm, the invariable combination of thoracic and abdominal symptoms and signs is readily understood.

Later, as the ectopic gastric juice continues to digest the mediastinal tissues, the surgeon (if he still carries a stethoscope) may be able to detect fluid at one or both bases, and he may occasionally hear a characteristic clicking sound that is due to air in the mediastinum. Or if he is very thorough and has a high index of suspicion, he may find subcutaneous emphysema in the neck or supraclavicular spaces. With a history of pain in the upper abdomen appearing after vomiting, the finding of subcutaneous emphysema in the neck is almost diagnostic of rupture of the esophagus. (It is not always present, however.)

The roentgenologist has occasionally made the diagnosis by discovering mediastinal emphysema on a film taken to determine the presence of air under the diaphragm. A film of the chest may also show hydrothorax, hydropneumothorax, mediastinal, cervical or supraclavicular emphysema. A conclusive diagnosis rests with the demonstration of a radiopaque fluid flowing through the opening in the esophagus into the mediastinum or pleural cavity.

Differential Diagnosis

When the three classic signs of rigid upper abdomen, dyspnea and subcutaneous emphysema are not present, when the subcutaneous emphysema has not been detected or when rupture of the esophagus is not considered, perforated peptic ulcer is most commonly the diagnosis. Many patients are first operated on abdominally because of an erroneous diagnosis of perforated peptic ulcer. Coronary thrombosis, pulmonary embolism, spontaneous pneumothorax, dissecting aneurysm of the thoracic aorta, acute pancreatitis, rupture of the diaphragm or incarceration of a diaphragmatic hernia, renal colic and acute cholecystitis have all been considered.

Surgical Treatment

After the diagnosis has been made, prompt action is necessary. For with the passing of each hour, corrosion of the mediastinum progresses, and infection of the mediastinal tissues sets in. Prompt resuscitative measures should be carried out before and while the diagnosis is being made to relieve the disastrous effect of prolonged hypotension. Prompt thoracotomy, under endotracheal anesthesia, with direct closure of the esophageal rent with two layers of interrupted fine-silk sutures, seems to offer the best hope of recovery. Our experience shows that thoracotomy with direct suture of the perforation can be performed with safety on critically ill, elderly, depleted patients in shock. The operation itself is one of the resuscitative measures.[3] The improvement in both cases reported above was striking after the mediastinum had been opened, the acid fluid removed, and the perforation sutured.

In patients who have survived the initial assault owing to smaller tears, less extensive digestion of

the mediastinum or localization of the fluid because of previous pleural adhesions, success has been achieved by closed drainage of the empyema. Appropriate antibiotic therapy, of course, should be instituted. A jejunostomy for feeding purposes at the time of the original operation was essential to recovery in Case 2. The continuation of Wangensteen suction with a Levin tube in the stomach through the esophagus is essential in the prevention of postoperative vomiting.

Summary and Conclusions

The clinical picture of sudden rupture of the esophagus caused by vomiting is characterized by rigidity and tenderness of the upper abdomen, difficulty in breathing, subcutaneous emphysema and shock. The diagnosis of rupture of the esophagus should be considered when there is uncertainty whether the pathologic process is above or below the diaphragm in patients presenting acute upper abdominal pain.

Once suspected, the diagnosis can be confirmed by the finding of mediastinal emphysema on a chest film, gastric fluid on thoracentesis or an opening in the esophagus after a barium swallow.

Delay is fatal. Prompt resuscitative measures followed by thoracotomy under endotracheal anesthesia, with primary suture of the esophageal tear, is the procedure of choice.

Two cases in elderly patients are reported. In 1 case primary suture was performed twenty-four hours after the rupture, and the patient survived for eight days. Death was due to mediastinitis and dissolution of the esophageal suture line. In the other case primary suture was performed six hours after rupture, and the patient recovered rapidly; later, he was found to have inoperable carcinoma of the stomach.

If the patient is not moribund and good anesthesia service is available, prompt primary suture of the esophageal tear offers the best chance of recovery.

References

1. Vinson, P. P. Oesophageal stricture following vomiting of pregnancy. *Surg., Gynec. & Obst.* 33:412, 1921.
2. Weiss, S., and Mallory, G. K. Lesions of cardiac orifice of stomach produced by vomiting. *J. A. M. A.* 98:1353-1355, 1932.
3. Samson, P. C. Postemetic rupture of esophagus. *Surg., Gynec. & Obst.* 93:221-229, 1951.

MEDICAL PROGRESS

LIVER BIOPSY (Concluded). II. THE RISK OF NEEDLE BIOPSY*

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Complications of Liver Biopsy

Most needle biopsies are free of complications. Klatskin[186] reported that more than 80 per cent of 352 needle biopsies were without mishap (Table 1). Terry,[186] reviewing 7532 biopsies noted 24 "significant" complications, an incidence of only 0.23 per cent.

Pain, the most frequent complication of liver biopsy, variously reported in 5 to 50 per cent of patients,[6] is usually short lasting and may be controlled readily by routine analgesics.[186] Perhaps, the best indication of this is the willingness of almost all patients to permit repeat biopsy. Multiple biopsies have been performed on many patients, as many as 6 within four weeks on 1[39] and 13 on another.[186] A confident, reassuring manner, a simple explanation of the procedure and careful application of local anesthesia minimize preoperative apprehension and subsequent pain.

A brief friction rub caused by fibrinous perihepatitis or pleuritis is occasionally heard over the liver after biopsy.[19] Pleural hemorrhage, effusion and pneumothorax may follow the transdiaphragmatic route. We have observed transfer of ascitic fluid through a perforated right leaf of the diaphragm into the thorax in 3 cases with mild respiratory embarrassment. Boucher et al.[197] reported pleural bile effusion in a patient with obstructive jaundice. Avoidance of the upper margin of the intercostal space minimizes the danger of perforation of an intercostal vessel. Despite the frequently asserted danger of perforating large diaphragmatic veins, no hemorrhages from this source have been reported.§

Penetration of abdominal viscera other than the liver or gall bladder is a rare complication of needle biopsy. Terry[186] found no report of this complication in reviewing 7532 needle biopsies performed since 1939. Baron[1] biopsied the colon without consequence. One alleged fatal case after accidental puncture of the colon was brought to the attention of Hoffbauer,[6] but no detailed description of this

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§A case with alleged bleeding from a diaphragmatic vessel has recently come to our attention. The patient died 18 hours after transthoracic biopsy, and the liver at autopsy contained both miliary tubercles and metastatic cancer. The fact that 1000 cc. of blood was found in the abdominal cavity and none in the pleural space raises some doubt about the diaphragm as the source of bleeding, however.

case has been found. Reynolds[108] refers to a similar case in which colonic mucosa was obtained on biopsy. There was no evidence of peritonitis or untoward sequelae, however, and laparotomy three days later revealed no site of puncture.

Perforation of the distended gall bladder[2, 22, 100] is also rare. Kleitsch and Kehne[200] believe that it results only from the unwarranted use of the abdominal approach to a liver that is either not palpable or only slightly palpable. Most workers are now agreed that this danger of the transabdominal approach to the liver precludes its routine use.

Table 1. *Complications Encountered in 352 Liver Biopsies.*[9]

Complication	No. of Patients	Percentage
None	291	82.6
Pain requiring analgesics	45	13.0
Fall in blood pressure	5	1.4
Low blood pressure requiring transfusions	3	0.8
Fever	3	0.8
Bleeding at biopsy site	3	0.8
Probable bile peritonitis†	1	0.3
Pleural effusion	1	0.3

*Based on data of Klatskin.[101]
†Surgical intervention not required.

Bile peritonitis, a serious complication of liver biopsy, results almost entirely from bile leakage from the dilated biliary passages of patients with obstructive jaundice.[100] Terry reported 11 cases of biliary peritonitis, 3 requiring laparotomy. Obstructive jaundice existed in 10 of these and had recently been present in the other.[102] Because of the hazard of this complication, biopsy is usually contraindicated in patients with known obstructive jaundice. Bile peritonitis from nonobstructive jaundice has not been reported. Neither Sherlock[9] nor Weisbrod[107] mentioned this complication in a total of 338 biopsies on jaundiced patients. Accordingly, clinical findings consistent with bile peritonitis occurring promptly after needle biopsy in jaundiced patients is prima-facie evidence of obstructive jaundice, and early laparotomy should be considered. Prompt decompression of the biliary passages is indicated.

Brown and Walsh[208] reported a fatal outcome in a markedly jaundiced patient after liver biopsy done in an attempt to distinguish between obstructive and intrahepatic disease. At autopsy, golden-brown pigment masses were found in many of the arteries of both lungs. These were interpreted by the authors as bile emboli. The entire biliary system was dilated. There was no microscopical evidence of primary liver disease.

Hemorrhage from the liver is the most frequent serious complication and the chief cause of death. Bleeding after biopsy has been observed to consist usually of a thin trickle from the puncture wound in the liver lasting ten to sixty seconds and totaling 5 to 10 cc.[88] Most cases of fatal hemorrhage have resulted from perforations of distended portal or hepatic veins or aberrant arteries (Table 2). In some cases a tear of the liver occurred when a patient breathed deeply during intercostal biopsy. The bleeding tendency and impaired blood coagula-

Table 2. *Causes of Death in 39 Cases after Liver Biopsy.*

Case No.	Author	Year	Cause of Death	Clinical & Autopsy Findings	Underlying Disease of Liver	Comment
1	Biagel[203]	1923[a]	Hemorrhage	Autopsy diagnosis, cancer of stomach, with extensive replacement of both adrenal glands by tumor and hemorrhagic infarction of remainder of adrenal glands	Not reported	No coagulation studies done; slow biopsy technic, now discarded; ? role of adrenal insufficiency in death.
2			Hemorrhage	Severe pernicious anemia (red-cell count, 500,000); patient breathed during intercostal insertion of needle.	Not reported	No coagulation studies; slow procedure used.
3	Olivet[203]	1926	Hemorrhage	Clinical & autopsy diagnosis, carcinoma of pylorus, with extensive metastases to liver, lymph nodes & adrenal glands (blood in peritoneal cavity did not coagulate on standing).	Metastatic carcinoma of liver	Death 2 hr. after biopsy; no prothrombin time determined before biopsy; author believes this to have been prolonged.
4			Hemorrhage	Clinical diagnosis, ? chronic lead poisoning and pernicious anemia (red-cell count, 575,000); autopsy revealed hemorrhage into peritoneal cavity.	Hemosiderosis	Patient in very poor condition; no transfusions given; no coagulation studies performed before biopsy in spite of patient's severe anemia; biopsy done through intercostal route and patient breathed during procedure, which resulted in tear of liver capsule; death 24 hr. later.
5			Peritonitis	Clinical diagnosis, hepatomegaly, undetermined cause; autopsy diagnosis, carcinoma of gall bladder, with extensive metastases to liver, subphrenic abscess and early peritonitis.	Metastatic carcinoma of liver, with subphrenic abscess	Signs of peritonitis soon after biopsy; patient died 36 hr. later; although not demonstrated, assumed that needle biopsy caused extension of infection from abscess to peritoneum; no chemotherapy available.
6	Tou'lec & Huard[203]	1935	Hemorrhage	No information	?	No evaluation possible.
7	Baron[3]	1939	Hemorrhage	Autopsy showed exsanguinating hemorrhage from 1-cm. tear in liver	Extensive metastatic carcinoma of liver	No coagulation studies done; patient breathed during procedure (abdominal route).
8	Koller[203]	1940	Hemorrhage	No information	?	No evaluation possible
9			Hemorrhage	No information	?	No evaluation possible

[a]The year given does not usually correspond to the actual year of death, which in most cases occurred one or more years previously. It corresponds either to the date of the report or to that when information was obtained for the purpose of this review.

TABLE 2 (*Continued*).

Case No.	Author	Year	Cause of Death	Clinical & Autopsy Findings	Underlying Disease of Liver	Comment
10	Roholm et al.[105]	1942	Hemorrhage	Clinical diagnosis, progressive jaundice; autopsy showed bleeding into peritoneal cavity	Carcinoma of head of pancreas, with obstructive jaundice	Operator admitted prothrombin activity not tested before biopsy, but later found to be very low; death 9 days after biopsy, with general signs of hemorrhagic diathesis.
11			Hemorrhage	Clinical diagnosis, long-standing jaundice; autopsy showed intraperitoneal hemorrhage	Metastatic carcinoma of hepatoduodenal ligament, primary, unknown	In spite of prolonged prothrombin time, vitamin K not administered before procedure, by oversight; death 10 hr. after biopsy.
12	Raby[107]	1944	Hemorrhage	Clinical diagnosis, jaundice of obscure origin	?	Death precipitated by biopsy (needle punctured superficial branch of portal vein); 1.5 liters of blood in peritoneal cavity (clotting time had been normal).
13			Unknown	No information	?	Death 3 days after biopsy; no proof that death caused by biopsy; no cause of death found at autopsy.
14	Davis[108]	1947	? Hemorrhage	Autopsy diagnosis, severe hepatic damage, with bile nephrosis	?	Pathologist's opinion that cause of death hepatic and renal failure rather than hemorrhage; patient not in shock and lost only 500 cc. of blood.
15	Bock[42]	1948	Hemorrhage	Clinical diagnosis, acute liver failure.	Widespread necrosis & hepatitis superimposed on fatty cirrhosis	Patient critically ill; death 3 hr. after 2d (interval) puncture, performed on uncooperative patient; marginal prothrombin time (50 per cent).
16	Griesemann[109]	1949	Hemorrhage	Autopsy showed injury to branch of portal vein without any tear of liver; 1.5 liters of blood in peritoneal cavity.	Long-standing subacute catarrhal icterus	Death unquestionably precipitated by biopsy
17	Hoffman & Rosenthal[50]	1950	Bile peritonitis	Autopsy showed bile peritonitis apparently caused by needle's entering obstructed & dilated intrahepatic biliary duct, producing coning and bile peritonitis	Apparently obstructive jaundice	Death 3 days after biopsy, which operator considered cause of death; no clinical or laboratory data given.
18	Gallico & Skinner[110]	1950	Bile peritonitis	Clinical diagnosis, jaundice & thrombocytopenia (equivocal laboratory tests); autopsy showed 8000 cc. of turbid, dark-yellow, watery fluid in peritoneal cavity.	Post-mortem findings included adenocarcinoma, Grade 2, of ampulla of Vater, with obstruction of common bile duct, pancreatic necrosis, slight, & portal and biliary cirrhosis	Death 7 days after & clearly related to biopsy
19	Moyer & Weri[111]	1951	? Hemorrhage	No bleeding point found at laparotomy or autopsy	Fatty metamorphosis, with passive congestion	History of repeated gastrointestinal hemorrhage; intra-abdominal bleeding developed; death 4 days after biopsy, which was not directly responsible; immediate cause of death, during laparotomy, considered "cardiac arrest" secondary to severe coronary-artery disease.
20	White (cited by Terry[112])	1951	Hemorrhage	None available	Advanced cirrhosis of liver	Low prothrombin time
21	Sherlock[43]	1952	Hemorrhage	Both patients moribund, with severe liver disease; 1 also had general paresis & rectal cancer.	One had acute & other subacute necrosis of liver	Patients already moribund; large-bore needle then used (now discarded).
22			Hemorrhage			
23	Gilman[52]	1952	Hemorrhage	Autopsy showed unusual artery in liver had been punctured (peritoneal cavity filled with blood)	Tuberculous hepatosplenomegaly	Patient suddenly collapsed 2 hr. after puncture, with signs of intraperitoneal hemorrhage; death unquestionably precipitated by biopsy.
24			Hemorrhage		Widespread hepatic carcinoma	Patient moribund at time of biopsy
25	Veiwiler & Jones[53] & Ellis[54](Massachusetts General Hospital)	1952	Hemorrhage	Autopsy showed large laceration extending entire length of rt. lobe (needle had pierced rt. main hepatic vein, leading to intrahepatic bleeding & splitting friable amyloid liver)	Amyloid disease	Severe abdominal pain; shock 10 hr. after biopsy which undoubtedly precipitated death; prothrombin time borderline (prolonged 6 sec.)
26			Peritonitis	Autopsy showed peritonitis (due to beta-hemolytic streptococcus), with septicemia.	Fulminating acute cirrhosis	Operators did not believe biopsy, performed 3 days before death, was cause of peritonitis; temperature chart gave no clue to time of onset of peritonitis.

TABLE 2 (*Concluded*).

Case No.	Author	Year	Cause of Death	Clinical & Autopsy Findings	Underlying Disease of Liver	Comment
27			Bile peritonitis	Autopsy showed obstruction of common bile duct by carcinoma	Obstructive jaundice	Death clearly related to biopsy
28			Hemorrhage	Autopsy showed large vein perforated, with 1500 cc. of blood in abdominal cavity	Oat-cell carcinoma, with metastases to liver	Patient went into shock; death clearly related to biopsy.
29	Klatskin[22]	1952	Hemorrhage	Autopsy showed large vein punctured by needle	Widespread lymphoma	Biopsy clearly cause of hemorrhage
30			? Hemorrhage; ? neurogenic shock.	Autopsy showed 2 1-cm. lacerations approximately 2 cm. in depth	Moderately severe hepatitis	Operator did not believe that shock was due to blood loss alone; patient given total of 3 liters of blood immediately & yet peritoneal cavity contained only 400 cc. of blood; death 3 hr., 25 min., after biopsy; patient took deep breath while specimen was being obtained & lacerations believed to have occurred at that time; ? neurogenic shock.
31	Rubenstone et al.[23]	1952	Bile peritonitis	Clinical diagnosis, obstructive jaundice; autopsy showed obstruction of common bile duct by precipitated putty-like material (cholangiectatic duct had been accidentally transversed).	Obstructive jaundice	Death 4 days after & clearly related to biopsy; 2000 cc. of bile-stained fluid in peritoneal cavity; culture showed *Escherichia coli* & *Bacillus subtilis*.
32	Armed Forces Institute of Pathology[24]	1952	Hemorrhage	Clinical diagnosis, carcinoma of hepatic flexure of colon (needle biopsy showed adenocarcinoma); autopsy revealed adenocarcinoma of head of pancreas, with metastases to liver.	Metastatic carcinoma	Patient went into shock & died from hemorrhage at site of biopsy, which probably precipitated death.
33			Hemorrhage	Clinical diagnosis of tuberculosis of spine & liver disease; autopsy showed tuberculosis of spine & amyloidosis of liver, kidney & spleen.	Amyloid disease (no amyloid found in section of liver from which biopsy was taken)	Death from hemorrhage 10 hr. after biopsy, which was considered cause of death
34	Brown & Walsh[25]	1952	? Bile embolism; ? neurogenic shock.	Clinical & laboratory findings not reported (bile aspirated with syringe during biopsy); autopsy showed severe obstructive jaundice, with greatly dilated gall bladder & biliary system, caused by carcinoma of ampulla of Vater; lung capillaries reported to contain bile; no hemorrhage found.	Bile stasis	Patient went into circulatory collapse & , despite transfusions, died 7 hr. after biopsy, which was undoubtedly related to death; mechanism obscure. Although case reported as fatal bile embolism, no mention of respiratory distress; impossible to evaluate case further because of paucity of clinical & absence of laboratory data.
35	Boston City Hospital[26]	1952	Hemorrhage	Autopsy showed liver laceration	Laennec's cirrhosis	Biopsy precipitated death in hopelessly ill patient, who was in terminal coma & breathed during procedure; low prothrombin time.
36			? Hemorrhage	Clinical diagnosis, widespread metastatic cancer of liver; no autopsy performed.	Metastatic cancer of liver	Biopsy contributed to death; low prothrombin time (40 per cent).
37	Wells[27]	1952	Peritonitis, purulent	Clinical diagnosis, icterus of several months' duration, with anemia & intestinal bleeding; autopsy showed carcinoma of bile ducts, with dilatation of biliary passages, subphrenic abscess & diffuse peritonitis.	Carcinoma of bile ducts	"At biopsy, infectious material apparently had been carried to the peritoneal cavity through puncture of a dilated bile duct"; (patient went into shock but recovered); several days later ileus developed, followed by death.
38	Rumball[28]	1952	? Hemorrhage; ? neurogenic shock.	Clinical diagnosis, extrahepatic biliary obstruction, with intense jaundice; autopsy showed 200 cc. of clotted blood over dome of liver & 250 cc. in pelvis.	Carcinoma of pancreas	Four hr. after biopsy patient went into shock & died shortly afterward; death apparently related to biopsy; operator believed that "actual amount of blood loss was insufficient to cause death; and although several theories have been advanced, no adequate explanation is apparent."
39	Marshall[29]	1952	Hemorrhage	Autopsy diagnosis, reticulum-cell sarcoma, with marked icterus, prothrombin time 65 per cent; autopsy showed 5000 cc. of blood in peritoneal cavity.	Reticulum-cell sarcoma	Three attempts made to obtain liver sample; 1 hr. after biopsy patient complained of abdominal pressure & desire to defecate; in spite of 2500 cc. of blood patient died 6 hr. after biopsy; death clearly related to biopsy; needle punctured 0.8-cm. vein situated 2 cm. below surface of liver.

tion associated with severe liver disease undoubtedly enhance the danger of severe bleeding.[219] Significant hemorrhage occurred 16 times, or 0.2 per cent, in 7532 biopsies.[198] Laparotomy was required in 4 patients, transfusion alone in 3, and expectant treatment in 9.

Kleckner et al.[220] reported 2 cases of transient "pleural shock" lasting one or two hours after biopsy. Inexplicable fatal shock has been described[223, 217] in at least 2 cases (Table 2): 1 patient, a sixty-seven-year-old man with severe homologous serum hepatitis,[223] was biopsied by a resident who had done at least 100 biopsies. The patient breathed deeply just as the specimen was being obtained through the ribs. Fifteen minutes later he went into shock. Transfusion was started immediately, and within half an hour an intra-arterial cannula was inserted, and a large volume of blood transfused under pressure. Despite the administration of 3 liters of blood, the blood pressure did not rise above 60 systolic, and the patient died three hours and twenty-five minutes after the biopsy. At autopsy, two 1-cm. lacerations, approximately 2 cm. in depth, were found in the liver. Surprisingly enough, the peritoneal cavity contained only 1 liter of liquid blood and 400 cc. of clotted blood (this volume of blood had been replaced within half an hour of the onset of bleeding). Nevertheless, the patient remained in shock and did not regain consciousness. In these cases the irreversible shock could not be explained on the basis of blood loss alone.

Implantation of tumor cells in the needle track has been reported.[221, 222] No case of air embolus has been reported although the theoretical possibility has been mentioned.[5]

TABLE 3. *Fatal Cases among 20,016 Needle Biopsies of the Liver.*

Author	Year of Report	No. of Biopsies	Alleged Fatal Cases
Schupfer[203]	1907	40	0
Binger[204]	1923	100	2
Olivero[205]	1926	140	3
Widenbrück[206]	1928	30	0
Toulier[207]	1935	163	1
Perla[208]	1935	66	0
Bacon[9]	1939	48	1
Zollinger[209]	1940	100	2
Ashdown[210]	1942	297	2
Beck[10]	1948	56	1
Capewell[211]	1949	403	0
Gutzmann[212]	1949	52	1
Hoffbauer[6]	1949	400	0
Hoffman[213]	1950	43	1
Hoar[7]	1950	1500	0
Richards[8]	1950	300	0
Caravati[214]	1950	300	0
Mayer[215]	1951	200	1
White[216]	1951	761	1
Davis[217]	1951	500	1
Ellis[218] (including Volwiler and Jones)	1952	750+	6
Sherlock[219]	1952	650	2
Haig[11]	1952	401	0
Schiff[220]	1952	1349	0
Klatskin[221]	1952	1064	1
Armed Forces Institute of Pathology[222]	1952	2000+	2
Gillman[223]	1952	1828‡	2
Boston City Hospital[224]	1952	400	2
Wolfe[225]	1952	400	1
Kumbo's[226]	1952	308	1
Marshall[227]	1952	655	1
Totals		15,274	34†
Additional series without fatal outcome [228-230, 232-235] including others [12, 13, 223-225] collected by Terry[226]		4,742	
Total		20,016	

*Reported in Terry's[226] series.

†In addition to these, reports of 5 cases are available but were not included because the authors failed to indicate the total numbers of biopsies performed (see Table 2).

‡Excluding 454 biopsies on baboons and other animals.

Mortality

The wide acceptance of needle biopsy throughout the world is due largely to its low mortality in qualified hands, which Sherlock,[223] in 1949, estimated to be 0.29 per cent in 3159 patients, and Gallison and Skinner,[199] in 1950, to be 0.35 per cent in 4911 cases. Omitting fatal cases occurring before 1939, Terry[226] calculated the mortality in 1952 to be only 0.12 per cent in 10,600 cases. Reviewing 20,016 needle biopsies since 1907 we found 34 alleged deaths, making a mortality of 0.17 per cent (Table 3). Five authors reported additional fatal cases without indicating the total number of biopsies performed. If these cases are included a maximum mortality of 0.194 per cent is obtained. Each case is summarized in Table 2. We are aware of the possibility of error in reviewing published case histories. Yet this is essential to indicate the true mortality of needle biopsy. Much has been learned in the past fifteen years since needle biopsy was reintroduced by Iversen and Roholm.[6] There has been a steady improvement in methods and in criteria for selection of patients. Thus, outmoded procedures for biopsy were used in some early cases. At least 7 of the fatal cases occurred before 1940, when tests for liver function and blood coagulation were less reliable. Facilities for blood transfusion were sometimes limited, and antibiotics unavailable. The frequency of bleeding tendencies in patients with severe liver disease[219, 224, 215] has only recently been re-emphasized. Fatal biopsy was performed on 9 patients who would now be considered relatively poor risks; 4 of these were moribund at the time of biopsy. Coagulation was known to be defective in 4 others, and 1 patient was clearly unco-operative. Re-evaluation of 3 other fatal cases was impossible because of insufficient or unavailable data. Of the

TABLE 4. *Re-evaluation of Reported "Fatal" Cases after Needle Biopsy of Liver.*

Cause of Death	Total No. of Patients	Fatalities Acceptable under Current Criteria		
		yes	no	?
1. Hemorrhage	25	9	16	
2. ? Hemorrhage	5	2*	2	1†
3. Bile peritonitis	4	4		
4. Suppurative peritonitis	3	1	2	
5. ? Bile embolism	1	1*		
6. Unknown	1			1
Totals	39	17	20	2

*? Neurogenic shock.

†Cardiac arrest.

39 fatalities (Tables 4 and 5) only 17 appeared acceptable when considered in the light of present knowledge. Excluding these cases the true mortality of 0.085 per cent is obtained (Table 6).

The large series reported by several of the most experienced authors confirm the fact that a mortality approaching zero is indeed possible. Thus,

TABLE 5. *Re-evaluation of 39 Fatal Cases Attributed to Needle Biopsy.*

REASON FOR EXCLUSION		No. OF CASES
Fatal cases before 1940		7
Death clearly unrelated to biopsy		3
Biopsy contraindicated		9
Patient moribund	4	
Coagulation defective	4	
Unco-operative patient	1	
Evaluation impossible because of incidental data		3
Fatal classification acceptable under current criteria		17
Total		39

Schiff[206] and his associates performed more than 1300 biopsies, and Haex[207] more than 1500 without a death. The experience observed at the Boston City Hospital is typical of that in many institutions. In 1945 needle biopsy was first introduced into the Harvard Clinical Unit. Two deaths occurred among

TABLE 6. *Adjusted Mortality in 20,016 Needle Biopsies of the Liver.*

CLASSIFICATION	No. OF CASES	PERCENTAGE
Gross mortality:		
Deaths occurring in reported series	34	0.170
5 additional isolated cases	39	0.194
Adjusted mortality:		
Deaths acceptable under current criteria	17	0.085

the first few biopsies performed. Both patients were terminally ill, 1 in hepatic coma and the other with widespread cancer. In retrospect, it is clear that the procedure was unduly risky in both patients. Since that time almost 500 biopsies have been performed by 4 members of this clinic without serious

TABLE 7. *Underlying Disease in 17 Cases Accepted As Fatalities.*

DISEASE	No. OF CASES
Obstructive jaundice	2
Carcinoma of ampulla of Vater	2
Carcinoma of common bile duct	2
Metastatic carcinoma of liver	2
Widespread lymphoma	2
Hepatitis	2
Amyloid liver	2
Carcinoma of pancreas	1
Tuberculosis of liver	1
Unknown	1
Total	17

complication.[216] No patient has required transfusion or laparotomy after biopsy.

Fatal complications occurred most commonly in patients gravely or hopelessly ill at the time of biopsy (Table 7). Nine of the 17 cases apparently acceptable as fatal were associated with carcinoma, 2 with amyloid disease, 2 with severe hepatitis and 1 with tuberculosis of the liver. Thus, it is apparent that even with the most discriminate use, a premature death may be precipitated by biopsy in patients with markedly depleted reserve.

There is abundant evidence that the frequency of serious complications, including death, is high in inexperienced hands. Unreported fatal cases are known to have occurred at the hands of inadequately trained personnel. Although needle biopsy is a relatively simple procedure to perform, it should not be undertaken casually. There is general agreement that its use should be reserved for those familiar with liver disease, and that training should be acquired under their supervision. The failure to appreciate these facts has sometimes led to disaster and has unduly prejudiced some clinics against the use of the method.

In the past the use of needle biopsy has often been limited by fear of its complications. It is now apparent that the most conservative application of the method results in a mortality approaching that of other accepted procedures, such as spinal puncture and anesthesia, abdominal and pleural paracentesis[208] and gastroscopy.[209] Additional study is necessary before one further defines the group of marginal-risk patients in whom the hazard of management without benefit of biopsy diagnosis may exceed the risk of biopsy itself.

PRECAUTIONS AND CONTRAINDICATIONS

The proper selection of patients as candidates for biopsy entails balancing the potential diagnostic value of the procedure against its possible risk to the patient. The following precautions and contraindications have proved useful in reducing this risk:

First of all is the importance of training and experience, which was emphasized above. The occasional performance of needle biopsy is not likely to give operators confidence. Since assurance of manner is essential for complete patient co-operation, a manifest lack of confidence increases the danger of the procedure.

Secondly, the patient must be co-operative and able to carry out simple instructions involving control of respiration, especially when the transpleural approach to the liver is utilized. He is advised that he may experience some pain, most or all of which can be eliminated during the procedure by local anesthesia. Sedation may be given routinely to patients who are not in impending liver failure: 50 to 75 mg. of Demerol injected ten to twenty minutes before biopsy has been found satisfactory in this clinic.

Thirdly, although some workers recommend routine typing and cross-matching of blood for all patients, it is the practice of others to reserve this precaution for the more seriously ill patients.

Parenteral administration of vitamin K may be given prophylactically when necessary before the performance of the procedure.

Fourthly, the size and position of the liver vary from person to person and must be defined by percussion, palpation and, when necessary, x-ray examination. When the exact location is obscured by masses, fluid or operative scars, it is unwise to proceed. Although ascites in small amounts may not hamper the procedure, large quantities should be removed before biopsy. The physician must always have a clear awareness of the relation of the point of his needle to the liver. Hit-or-miss insertion of the needle is never justified, and clearly admits confusion. The percussion flatness of unexpected pleural or subdiaphragmatic fluid is sometimes mistaken for that of the liver, with consequent malpositioning of the biopsy needle.

Fifthly, to make correct decisions about the use and timing of needle biopsy familiarity with clinical liver disease in its many ramifications is imperative. The procedure itself may occasionally have to be altered during performance. For example, failure to meet the firm resistance of an anticipated cirrhotic liver may suggest reposition of the needle to the experienced operator, but may invite the neophyte to hazardous deeper insertion. Similarly, a soft, fatty or necrotic liver may offer so little resistance that it may induce the unsuspecting physician to make an unnecessarily deep penetration. Failure to meet liver resistance may confirm the clinical suspicion of a shrunken liver.

Sixthly, chronic passive congestion of the liver has been considered by some as a relative contraindication.[47] Sherlock,[27] however, has performed biopsies on 50 patients with chronic passive congestion without complication.

Seventhly, the presence of suppuration in the areas of approach to the liver contraindicates needle biopsy. Whenever we have unexpectedly encountered accumulations of pus in the pleural or subdiaphragmatic spaces, efforts to pierce the liver at that site have been discontinued. Because of the diagnostic importance of such unexpected findings, a sterile tube is included in the routine kit for collection of pus.

Eighthly, the small or nonpalpable liver may be difficult to biopsy, and a few workers[47] consider this a contraindication. We do not share this view.

Ninthly, enthusiasm for the use of liver biopsy has introduced the danger that it may be considered a substitute for complete clinical and laboratory work-up. This is clearly unwarranted.[67] The procedure should not be used until study by usual methods has been completed.

Tenthly, since the risk of biopsy is increased in the presence of jaundice, the selection of such patients is particularly important. Needle-biopsy confirmation of obvious extrahepatic obstructive jaundice is unwarranted. Sherlock[210] tends to avoid biopsy in the presence of deep jaundice, and Molle[47] is reluctant to biopsy any jaundiced patient. The decision in a given case of jaundice must be made on an individual basis. Most workers agree that the advantages accruing to the jaundiced patient far outweigh the risk.

Eleventhly, in general, liver biopsy is contraindicated in patients manifesting bleeding tendency or impaired blood coagulation. Most workers require a prothrombin time of 50 per cent or better before performing needle biopsy. Although this value was arbitrarily established, it has proved generally reliable. It may not guarantee freedom from bleeding in all cases, however. Because of the known vagaries of the one-stage prothrombin determination, the usual method for determining prothrombin time, we are prone to disregard a normal prothrombin time when there is evidence of clinical bleeding. Severe liver disease is regularly associated with abnormalities in hemostasis related in part to prothrombin deficiency, increased capillary fragility, diminution in platelets and sometimes vitamin C deficiency. The complexity of the problem of hemostasis has been emphasized in recent years.[210, 224] The evaluation of a given patient with abnormal bleeding may require extensive laboratory tests. Probably the most useful single laboratory technic is the silicone-clotting determination, which tests the coagulation of whole blood. Unfortunately, this procedure cannot be performed in a routine manner. Normal clotting time in glass tubes is not sufficient by itself to exclude the possibility of abnormal bleeding. Unless reliable laboratory tests for blood coagulation are available, erroneous determinations may give clearance for liver biopsy when the procedure is actually contraindicated. Thus, we have refused requests for needle biopsy despite apparently normal laboratory findings when the patient exhibited purpura or unexplained bleeding. Patients should be questioned routinely for easy bruisability and excessive bleeding from the nose, rectum or vagina. The skin should be examined for petechiae, purpura and ecchymoses, especially at the site of needle injections. Urine and stool specimens should be tested for occult blood. We have abandoned the performance of needle biopsy when bleeding from the routine nick of the skin before the actual introduction of the biopsy needle was unduly prolonged.

In rare cases the risk of needle biopsy may be warranted in certain patients who do not satisfy these criteria. A prothrombin time of 50 per cent may not differ enough physiologically from one of 35 per cent to warrant absolute discriminatory significance. We have performed needle biopsy in patients with prothrombin times of less than 50 per cent after careful evaluation of other coagulation factors. This should not be done,

however, without advice from specialists in blood coagulation. Differing from many workers, Whitesell and Snell[189] believe that in certain purpuric patients liver biopsy is indicated when necessary to distinguish between idopathic thrombocytopenic purpura, for the treatment of which splenectomy may be required, and thrombocytopenia secondary to liver disease, in which splenectomy may be contraindicated. They performed liver biopsies without mishap on 4 patients despite thrombocyte counts reduced to 43,000, 62,000, 67,000 and 75,000, and prothrombin times prolonged to 21 to 25 seconds (compared with normal values of 19 to 20 seconds).

Finally, careful follow-up observation should be made after every needle biopsy. Frequent pulse and blood-pressure readings may give early evidence of bleeding and permit prompt transfusion. Similarly, minimal signs of peritonitis may suggest bile leakage in jaundiced patients, and prompt exploratory laparotomy, with decompression of the biliary tree, may be instituted. Difficulty encountered during the procedure of needle biopsy should alert the physician to the possibility of complication.

Conclusions

A review of 20,016 needle biopsies of the liver indicates clearly that at present this is the most useful adjunct available for the diagnosis of clinical liver disease. In the hands of unqualified persons, misled by its apparent simplicity, the procedure is hazardous, but, when performed by experienced personnel, it is remarkably safe, having a true mortality of less than 1:1000. The proper use of needle biopsy can save many lives by permitting early diagnosis and prompt institution of correct medical or surgical therapy.

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References

194. Klatskin, G. Personal communication.
195. Terry, R. Risks of needle biopsy of liver. *Brit. M. J.* 1:1102-1105. 1952.
196. Sbarra, V. M., and Bluemle, L. W., Jr. Tetraethylammonium chloride in pain following liver biopsy. *U. S. Armed Forces M. J.* 1:545-549, 1950.
197. Boucher, R., Bernier, P., Lamarre, R., and Trempe, L. Ponction-biopsie du foie compliquée d'une péritonite suivie d'un épanchement pleural biliaire. *Bull. et Mém. Soc. Méd. d. Hôp. de Paris* 68:724, 1952.
198. Reynolds, W. S. Discussion of Stone, C. T., Jr., and Grater, W. C. Needle biopsy of liver (critical appraisal). *Texas State J. Med.* 46:825, 1950.
199. Gallison, D. T., Jr., and Skinner, D. Bile peritonitis complicating needle biopsy of liver. *New Eng. J. Med.* 243:47-50, 1950.
200. Kleitsch, W. P., and Kehne, J. H. Contraindications to punch (aspiration) biopsy of liver. *Am. J. Digest Dis.* 17:118, 1950.
201. Brown, C. Y., and Welch, G. C. Fatal bile embolism following liver biopsy. *Ann. Int. Med.* 36:1529-1533, 1952.
202. Biagi, A. Über die Parenchympunktion der Leber. *Verhandl. d. deutsch. Gesellsch. f. inn. Med.* 38:310, 1923.
203. Olivet, J. Die diagnostische Leberparenchympunktion. *Med. Klin.* 22:1640-1643, 1926.
204. Toullec, J., and Hirard, P. La ponction exploratrice du foie. *Monde méd., Paris* 48:990-999, 1938.
205. Kofler, W. Die Leberpunktion als bewährtes und wertvolle klinische Untersuchungsmethode. *Ztschr. f. klin. Med.* 138:744-753, 1940.
206. Roholm, K., Krarup, N. B., and Iversen, P. Aspirationsbiopsie der Leber. Mit einer Übersicht über die Ergebnisse bei 297 Biopsien. *Ergebn. d. inn. Med. u. Kinderh.* 61:635-679, 1942.
207. Raby, K. Complications and dangers of liver biopsy. *Nord. med. tidskr.* 26:2161-2174, 1948.
208. Davis, W. D., Jr. Needle biopsy of liver. *New Orleans M. & S. J.* 100:159-163, 1947.
209. Griesmann, H. Über die Leberpunktion. *Zentralbl. f. Chir.* 76: 917-920, 1949.
210. Sherlock, S. Personal communication.
211. Gillman, T. Personal communication.
212. Ellis, D. S. Personal communication.
213. Klatskin, G. Personal communication.
214. Rubenstone, A. I., Mintz, S. S., and Moreano, D. R. Case of fatal bile peritonitis following liver needle biopsy. *Ann. Int. Med.* 36:168, 1952.
215. Registrar of the Registry of Hepatic Pathology, Armed Forces Institute of Pathology, Washington, D. C., 1952. Personal communication.
216. Chalmers, T. C., Davidson, C. S., Zamcheck, N., and Phillips, G. Unpublished data.
217. Rumbell, J. M. Needle biopsy of liver: analysis of 308 cases. *Am. J. Surg.* 84:131-140, 1952.
218. Marshall, D. Liver biopsy complicated by occult intra-abdominal bleeding leading to death: report of case. *Gastroenterology* 23: 119-123, 1952.
219. Prommeyer, W. B., Jr., and Epstein, R. D. Hemorrhagic diseases. *New Eng. J. Med.* 241:700-712 and 743-750, 1949.
220. Klechner, M. S., Jr., Stauffer, M. H., Bargen, J. A., and Docherty, M. B. Hepatic lesions in living patient with chronic ulcerative colitis as demonstrated by needle biopsy. *Gastroenterology* 23: 13-33, 1952.
221. Sapper, I. Discussion of Rappaport, E. M. Liver biopsy. *Rev. Gastroenterol.* 18:643-650, 1951.
222. Sommerfelt, S. C. Malignant hepatoma with implantation metastasis following liver puncture. *Nord. med. tidskr.* 46:1492-1494, 1951.
223. Sherlock, S. Puncture biopsy of liver. *Univ. West. Ontario M. J.* 19:133-135, 1949.
224. Desforges, J. F., Bigelow, F. S., and Chalmers, T. C. Effects of massive gastrointestinal hemorrhage on hemostasis. I. Blood platelets. II. Blood coagulation. *J. Lab. & Clin. Med.* (in press).
225. Palmer, E. D., and Brick, I. B. Sources of upper gastrointestinal hemorrhage in cirrhotic patients with esophageal varices. *New Eng. J. Med.* 248:1057, 1953.
226. Schiff, L. Personal communication.
227. Haex, A. J. C. Der biopsie van der lever. *Nederl. tijdschr. v. geneesk.* 94:3077-3076, 1950.
228. Schupfer, F. De la possibilité de faire "istravitam" un diagnostic histo-pathologique précis des maladies du foie et de la rate. *Semaine méd. Hôp. de Paris* 27:229, 1907.
229. Waldenström, H. Formation and disappearance of amyloid in man. *Acta chir. Scandinav.* 63:479-530, 1928.
230. Frola, E. *Il puntato epatico nella diagnosi delle malattie del fegato.* 216 pp. Roma: Luigi Pozzi, 1935.
231. Tripoli, C. J., and Feder, D. E. Differential diagnosis of certain diseases of liver by means of punch biopsy. *Am. J. Clin. Path.* 11:516-527, 1941.
232. Chiray, M., Fiessinger, N., and Roux, M. La ponction-biopsie du foie. *Presse méd.* 49:785-788, 1941.
233. Aszenfeld, H., and Brase, K. Klinische und bioptische Untersuchungen über die sogenannten Icterus catarrhalis. *Ztschr. f. Path.* 57:147-236, 1942.
234. Hatieganu, I., Sparchez, T., Radu, P., and Macavei, I. Der Wert der Leberpunktion in der Diagnose der verschiedenen Lebererkrankungen. *Wien. klin. Wchnschr.* 86:21, 1943.
235. Post, J., Benson, J. G., and Brakeman, P. Observations on cytoplasmic hepatic-cell pigment in man. *Arch. Path.* 53:67-72, 1951.
236. Seife, M., Kessler, B. J., and Lisa, J. R. Clinical, functional and needle biopsy study of liver in alcoholism. *Arch. Int. Med.* 86: 658-670, 1950.
237. Kubicki, S. T. Wartosc kliniczna naklucia watroby. *Polski tygodnik lek.* 6:507-513, 1951.
238. Cassel, C., Bone, F. C., Ruffin, J. M., and Stoddard, L. D. Evaluation of liver biopsy as diagnostic procedure. *Am. Pract. & Digest Treat.* 2:745-754, 1951.
239. Tsung, H. L. Bile peritonitis following liver biopsy with recovery. *New York State J. Med.* 52:766, 1952.
240. Grady, J. J. Needle biopsy of liver. *Ohio State M. J.* 48:730-733, 1952.
241. Aronson, W., Di Lorenzo, J. C., and Katz, E. Diagnostic value of liver punch biopsy. *New York State J. Med.* 51:2523-2526, 1951.
242. Meitus, M. L. Experience with liver biopsies in private hospital. *Ohio State M. J.* 48:515-517, 1952.
243. Klechner, M. S., Jr., Stauffer, M. H., Bargen, J. A., and Docherty, M. B. Hepatic lesions in living patient with chronic ulcerative colitis as demonstrated by needle biopsy. *Gastroenterology* 23: 13-33, 1952.
244. Plaucche, M. B., Schier, R., Loisy, C., and Chastel, J. Des données de la ponction-biopsie dans les hépatomégalies de l'Européen ayant séjourné en région tropicale ou subtropicale. *Lyon méd.* 186:33-44, 1952.
245. Morland, A. Pleural shock. *Lancet* 2:1031-1033, 1049.
246. Boyden, E. A. *Radiography as Related to Diseases of the Bronchus.* 373 pp. Baltimore: Williams & Wilkins, 1951.

MEDICAL INTELLIGENCE

ISONIAZID IN TUBERCULOUS PSYCHOTIC PATIENTS

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NORWICH, CONNECTICUT

WHEN isoniazid (iso-nicotinic acid hydrazide) was first introduced in the treatment of tuberculosis, it was noted that, in contrast to other antituberculosis drugs, it was of low toxicity. Such toxic manifestations as were observed in the early days of its use (involuntary twitching, hyperreflexia, irritability, transient loss of memory, constipation, vertigo, insomnia and difficulty in starting the urinary stream) were transitory and mild, even with the continued use of the drug, and little clinical significance was attached to them. However, with more patients receiving the drug and with increases in dosage, it became apparent that isoniazid could have serious toxic effects. Acute pellagra[1] and polyneuritis[2] have been reported. One of us (M.A.F.) has seen 2 patients who became acutely psychotic and returned to normal with the prompt discontinuance of the drug. Hunter[3] reports a case of confusional psychosis due to isoniazid therapy in which organic cerebral impairment of the Korsakow type remained. The larger doses are not necessarily the cause, for reports from Sweden[2] show that psychotic episodes occurred in patients receiving 4.3 mg. of isoniazid daily per kilogram of body weight.

When it became apparent that isoniazid produced toxic manifestations affecting mainly the central nervous system, some physicians[4] even advocated withholding the drug in patients with organic disease of the central nervous system or with abnormal mental or emotional signs or history. It was decided, therefore, to try to determine the effect of isoniazid on tuberculous patients who were also psychotic. It was not possible, as a control, to administer the isoniazid to a similar group of mentally ill patients who were not tuberculous.

Accordingly, 39 mentally ill, tuberculous patients at the Norwich State Hospital were given isoniazid alone as treatment for their tuberculosis of the lungs for six months, from October, 1952, to April, 1953. The daily regimen consisted of 8 mg. of isoniazid per kilogram of body weight given in equally divided doses, twelve hours apart.‡

Laboratory studies, made before drug therapy and every two months during the study, included the following: complete hemogram, determination of blood urea nitrogen, urinalysis and single posteroanterior roentgenograms of the chest. Sputums were examined once a month for acid-fast bacilli by smear, or culture, of a concentrate of a seventy-two-hour pooled specimen or by culture of gastric specimens. The patients were weighed once weekly.

TABLE 1. *Age Distribution.*

AGE	NO. OF PATIENTS
yr.	
20–29	2
30–39	5
40–49	6
50–59	10
60–69	11
70–79	3
80–89	1
90–99	1

TABLE 2. *Types of Psychoses Encountered.*

TYPE OF PSYCHOSIS	NO. OF PATIENTS
Schizophrenic reaction:	
Paranoid type	9
Simple type	2
Hebephrenic type	3
Undifferentiated type	3
Catatonic type	2
Paranoid reaction:	
Paranoia	1
Paranoid state	2
Manic-depressive reaction:	
Depressed type	2
Other	1
Involutional psychotic reaction	1
Mental deficiency, idiopathic, severe	1
Chronic brain syndrome associated with convulsive disorder, with psychotic reaction	1
Sociopathic personality, dyssocial reaction	1
Organic brain disease, with various etiologic factors	6
Total	39

Of the 39 patients, 25 were men, and 14 were women; 2 were Negroes, and 37 whites. The ages ranged from twenty-nine to ninety-three (Table 1).

The types of psychoses dealt with and the number of patients are shown in Table 2. The duration of mental illness before the start of isoniazid therapy ranged from six months to fifty years, the average being fourteen years.

The tuberculosis was minimal in extent in 8, moderately advanced in 17 and far-advanced in 14

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‡At the start of the study at Norwich State Hospital, the average dosage used in tuberculosis work was 6 mg. per kilogram of body weight. However, in a paper presented by McDermott and his associates at the Connecticut Clinical Congress in New Haven in September, 1952, the results of 5 to 10 mg. in 25 cases of miliary and meningeal tuberculosis were stated to have been so good that the 8-mg. amount was adopted as the standard dose. Since, at the time of the study, there was no definite correlation between high dosage and toxic reactions, it was decided to use the 8-mg.-per-kilogram regimen in view of McDermott's excellent results.

patients. The tuberculosis was diagnosed from three months to twenty-seven years before the start of drug therapy, the average being eight years. All types of tuberculosis were seen: exudative, nodular, fibrotic, calcific, caseous, cavitary and mixed. In all but 2 cases the sputum was positive for acid-fast bacilli at the start of the study, and these 2 patients had in the past produced acid-fast bacilli. Six patients had had streptomycin alone or in combination with para-amino-salicylic acid from three months to one year before the institution of isoniazid therapy.

Somatic therapy for the mental illness was used when indicated during the course of drug therapy.

Discussion

The sputum of 14 patients converted from positive to negative and was still negative three months after cessation of drug treatment. Five of these 14 had cavitary disease, and none of the 14 showed any significant change on x-ray examination.

Of the 39 patients, x-ray study demonstrated no significant change in 32, slight improvement in 3, moderate improvement in 1 and marked improvement in 2. One patient had slight increase in disease. Of the 6 patients with some x-ray improvement, the sputum remained positive in 5 and converted to negative on smear of concentrate in the other.

Except in 1 patient, no serious toxic manifestations were observed that could be attributed to the use of isoniazid.

So far as the lesser side effects of isoniazid are concerned, the patient with the diagnosis of involutional psychotic reaction showed definite euphoric changes. He became less depressed and less agitated a short time after taking isoniazid. Final evaluation was not possible because a prefrontal lobotomy was performed four months after the start of isoniazid therapy.

The greater portion of patients experienced a sense of well-being, which became apparent soon after the start of the drug therapy but lasted only a few weeks. With few exceptions, the patients showed an increase in appetite and gained from 1 to 1½ pounds a week throughout the study. Those not showing this response had been mentally ill for many years and were very regressed.

One patient, a fifty-three-year-old man, had had simple schizophrenia since 1936. He had been practically normal for at least ten years before the use of isoniazid, the only deviation from normal being a diminished affectivity. Two and a half months after the start of drug therapy, he had delusions and hallucinations, neither of which had ever been a part of his mental behavior in the past. This behavior persisted for the last three and a half months of drug treatment. When the drug was discontinued, his active psychotic symptoms were somewhat attenuated, but he continued to react to auditory hallucinations and was still somewhat delusional two and a half months after cessation of therapy.

Because of this, and because of the previous reports and experience as mentioned above, we do not believe that isoniazid is an innocuous drug. It is a potent and useful antituberculous agent, but toxic manifestations involving the central nervous system can occur and should be watched for. When they are present prompt discontinuance of the drug should be seriously considered.

Summary

Thirty-nine tuberculous psychotic patients were given a daily dose of 8 mg. of isoniazid per kilogram of body weight for six months. The sputum of 14 converted to negative. X-ray study showed some x-ray improvement in 6, some worsening in 1 and no change in 32 cases.

One patient, who had been practically normal mentally for ten years before isoniazid therapy, became delusional and hallucinated for the last three and a half months of drug treatment. He did not return to his previous mental status when the drug was discontinued.

References

1. McConnell, R. B., and Cheetham, H. D. Acute pellagra during isoniazid therapy. *Lancet* 2:959, 1952.
2. Foreign Letters, Sweden. Treatment of tuberculosis with isoniazid. *J. A. M. A.* 153:473, 1953.
3. Hunter, R. A. Confusional psychosis with residual organic cerebral impairment following isoniazid therapy. *Lancet* 2:960-962, 1952.
4. Anderson, R. J. New antituberculosis drug? *Pub. Health Rep.* 67:848-850, 1952.

BY THE LONDON POST

Smog and Anti-Smog—Iced Lollies—Christmas in the Wards

John Lister, M.D.

London, England

As the first anniversary of the disastrous fog of last December appears, the smog consciousness of the nation seems to be reaching a climax. Even through the autumnal "season of mists and mellow fruitfulness," the patients with chronic bronchitis have been thronging their doctors' offices, acutely anxious lest pneumonia supervene, and now, almost daily, there are columns and news items in the national press on the subject of Smog and Anti-Smog. A boom in the sale of surgical gauze and chiffon scarves resulted from the advice of the local Medical Committee of the County of London that the public should protect itself from fog by wearing a simple mask. The committee suggested that one could make an adequate mask, costing only a few pence, by folding strips of gauze into several layers, but the Minister of Health, Mr. Macleod, was quick to denounce the value of such a simple and cheap remedy. Asked in the House about prospective re-

search into the use of suitable respirators to combat thick fog, he said that although gauze masks would impede some of the solid particles, they would be of little value in absorbing toxic gases present in fog, such as sulfur dioxide. He also pointed out that respirators giving protection from gases had been known for many years, but the persons most affected by these gases were sufferers from chronic pulmonary or cardiac disease and special research was being carried out among the outpatients of a large hospital to determine what respirators could be safely worn by such persons for long periods. Despite the Minister's rejection of the simple mask many London drugstores were sold out of surgeons' gauze masks when the first heavy fog hit the City. A woman even bought one for her dog!

At the Royal Sanitary Institute, London, an exhibition demonstrates, with the help of working models, the formation of fog and its effect on health and buildings. Dr. E. T. Wilkins, research scientist to the Institute and officer-in-charge of the Department of Scientific and Industrial Research, has stated that final figures indicate that a total of 12,000 deaths could be attributed to last year's fog. In an illustrated lecture he showed charts of smog density during the foggy period and claimed that domestic fires are responsible for 60 per cent of smoke in winter. He pressed for more smokeless fuels, smokeless zones on the downwind side of polluted areas and perfected methods of banking up fires at night.

In leading articles the *Lancet* and *British Medical Journal* both stress the simple fact that Londoners manufacture their own fogs with the help of the weather and point out that they can overcome the fog menace only by producing less smoke. This has long been the contention of the National Smoke Abatement Society, and the enforcement of smokeless zones is long overdue. They were first suggested in this country by a Manchester barrister, Mr. Charles Gandy, in 1935, when he was chairman of the Smoke Abatement Society. By 1938 Manchester had planned a smokeless city center, but the war held up the scheme, which was not put into effect until 1952. The experiment has met with great success, and many other towns have obtained authority to impose restrictions on smoke. In particular, the City of London recently announced its intention of seeking statutory powers to establish a smokeless zone within the City. In such a zone the emission of smoke from any building is prohibited, but the ban does not cover railway locomotives. The creation of these zones is not without difficulties, since many interests are concerned. To overcome resistance it is necessary to show the public not only that smoke is a harmful nuisance but also that it is indicative of waste. Owners and tenants of premises within proposed zones must be consulted, and expert advice made available to them on any necessary conversion of fuel-burning appliances.

Whatever the opposition to the extension of smokeless zones, it is incumbent on the medical profession to press for them wherever local industrial and local weather conditions are likely to conspire to cause smog. It certainly looks as though the days of the English coal fire were numbered.

• • •

When I visited the United States I was greatly taken with the Howard Johnson hoarding advertising the sale of ice cream in 28 flavors. I cannot recall whether these flavors included anything resembling the iced lolly we know over here. I rather doubt it, for not only have these water ices mounted on sticks no food value but also certain of their species have recently been shown to contain significant amounts of copper, zinc and lead.

When asked in Parliament to set a national standard for iced lollies, Dr. Charles Hill, Parliamentary Secretary to the Ministry of Food, had first to define the lolly. He explained that it is "water with a fruit flavour that has been frozen" and not, as one member surmised, "a lollipop with the pop taken out."

Interest in the lolly was first aroused by the report of Semple in 1953 that these fashionable confections of varied and often hideous hue may contain up to 11 parts per million of lead. Copper, tin and zinc may be present in amounts up to 11, 7 and 5 parts per million, but these concetrations are not high enough to be harmful. On the other hand, the concentration of lead is undesirably high and could conceivably cause lead intoxication if sufficient lollies were consumed. It has been shown that the chief source of the lead is in the molds in which the water and colored syrups are frozen. Consequently, it is clear that one may prevent contamination by ensuring that only suitable nonmetallic containers are used in the preparation of the lollies, and it seems reasonable to make it illegal to sell lollies containing lead in a higher concentration than that found in the local drinking water.

Nevertheless, reviewing the situation in the light of the evidence, a cynical doctor remarked that it might do people less harm if they "left the lollipop and swallowed the stick."

• • •

Weeks before Christmas there were signs of preparation in the wards. Decorations were made by patients; lamp shades of crepe paper were cut out, and Christmas tree trinkets collected. On Christmas Eve the decorations go up, the trees are trundled in, and there is fierce competition among the nursing staff to see which ward will be acclaimed the best decorated. Indeed, when work is completed each ward looks more like a children's mystery corner in a Department Store than part of a hospital. Before the lights are finally dimmed, the carol party of nurses and doctors tours the hospital and

then all is quiet until Christmas morning, when Santa Claus (usually one of the interns) visits each ward fully clad in scarlet robes and distributes the patients' gifts. During the morning it is customary for all the doctors who normally work in the ward to make "Grand Rounds" with their wives and children, and there is usually a gift on the tree for every young visitor.

At mid-day comes the climax, when the turkey is ceremonially carved by a senior surgeon or physician who wears a chef's apron and hat for the occasion. After the Christmas dinner the postprandial stupor is profound, but the party is not yet over, for, later in the day, the interns entertain the patients in song and jest, which is usually at the expense of the more senior members of the hospital staff. Although next day the diabetic patients may show sugar, the gastric patients complain of discomfort and the temperature charts reveal an undulant fever, most patients will agree that they have never had a better Christmas than the one they spent in the hospital.

CONSULTANT'S OPINION

THE following letter has been submitted to the *Journal* by Dr. Robin Smith, of Neenah, Wisconsin.

It was sent nearly a hundred and one years ago, to the day, to his great-grandfather, Dr. N. S. Robinson, then a practitioner in Dover-Foxcroft, Maine.

The consultant in the case of Mrs. Hudson was almost certainly Dr. Walter Channing, who was admitted to the Massachusetts Medical Society in 1814, retired in 1854 and died in 1876 at the age of ninety.

Dr. Channing, one-time treasurer of the Society, was a founder of the *New England Journal of Medicine and Surgery* in 1812 and one of its first editors.

Boston, December 26, 1852

Dr. Robinson — Dear Sir —

I have examined the case of Mrs. Hudson. She has for some years suffered from pain in the right side, increased by lying on that side, and by pressure. I cannot detect any enlargement of the liver, and the pain is above its ordinary seat. There has been no functional disturbance of the organ, no deficiency of bile . . . by yellowness of the skin, or of the conjunctiva. Under these circumstances may we not regard it as a voracious modification of neuralgia, rather than dependent on organic union of any organ. In view of this I have thought that a treatment which would meet both in directions, whether of neuralgia or chronic hepatic trouble may be tried. I would recommend sponging the side once or twice a day with the nitro-muriatic bath, say with water made as acid as common vinegar. I would advise the wearing of flannel to prevent injuring the skin by the acid. This may be continued some time, . . . its advantage may be derived from its counter-irritant power, and from its specific agencies.

The uterus was carefully examined by touch and by speculum. There is normal *tenderness*, either *in it*, or in the region of the ovaries. But there is ulceration above, and in the os, and a dense, inspissated leukorrheal discharge, around and exuding from it. For this the nitrate of silver in solution or substance may be very carefully applied. I applied the former fully, and its effect may be noticed by her *sensations*, and by examination. The discharge should be carefully washed off by sponge and water, or a brush before the nitrate is used. The back, hips and lower part of the abdomen may be carefully rubbed once a day with a strong brine of salt and water.

For the trouble in the *side*, I would recommend a slightly alternative and tonic pill as follows:

Rx: Quinine sulphate: drams i
Extract comii : grains x
ext. Tanaxii : grains ii

M ft. pic. no. XX
one three or four times a day.

If heart be troubled by the pill, give it only twice or thrice a day, and half instead of a whole pill.

Exercise, moderate, or not reaching fatigue.

Diet. Morning and evening meals. Shells, or cocoa, fresh butter; an egg or two.

Dinner. Some meat if well digested. Avoid tea, coffee, cake, pastry, and all indigestible food.

I have thus gone into some detail. (The nitrate I meant to say may be applied twice a week.) I trust you will pardon me for minuteness in regard to remedies, and the mode of exhibition above suggested. I knew of no better way of stating exactly what a case submitted for consultation may seem to require. Still the adoption of some suggestions must always depend on the views taken of them by him to whom they are made. I submit them entirely to your judgment.

Accept my best thanks for the confidence reposed in me by your recommendation of Mrs. H. to my examination, and believe me when I add that I shall always be happy to hear from you, and of your success.

I remain yours very truly,

DR. CHANNING

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 39521

PRESENTATION OF CASE

A seventy-six-year-old retired stagehand was admitted to the hospital because of increasing dyspnea and paroxysms of coughing.

The patient had given up touring in road shows at the age of forty-six years because of an annoying morning cough, which was productive of "chunks" of yellow sputum. At this time allegedly moderate exertional dyspnea appeared, apparently persisting thereafter. Despite these symptoms he worked intermittently without much difficulty until about seven months before admission. There had never been any cyanosis, hemoptysis or chest pain. For a number of years he had preferred to sleep on two pillows. During the six months preceding admission he had noted some increase in severity of dyspnea but had done fairly well except for anorexia until about four weeks before entry. At that time there was the onset of what he interpreted as a "chest cold," characterized by markedly increased cough, dyspnea and orthopnea. Approximately three weeks before admission he began to experience bouts of paroxysmal nocturnal dyspnea with "wheezing." A week later he consulted his physician, who told him that he had a "tired heart" and placed him on digitoxin, Mercuhydrin, ammonium chloride, penicillin and streptomycin. About four or five days after the initiation of this therapy pedal edema developed, and the cough became more frequent and productive of "bubbly," whitish-yellow sputum that was not blood-tinged. By this time he was severely orthopneic. Five days before and on the night preceding admission he had suffered bouts of severe paroxysmal nocturnal dyspnea.

There was no history of chills, fever, night sweats, weight loss or chest pain either in the past or during the more recent phase of his illness. He had had occasional brief episodes of precordial "oppression" seemingly brought on by coughing or emotional upsets. The past history was otherwise noncontributory except for a two weeks' illness in 1918, when he was forty-one years old, diagnosed as pneumonia. The patient's wife had died three years previously of pulmonary disease manifested clinically by increasing cough and dyspnea; roentgenograms of the chest had revealed a "dense, honey-combed" appearance of the entire left lung, with numerous shadows interpreted as cavities, but attempts to establish the etiology were unsuccessful.

Physical examination revealed a ruddy-faced, markedly dyspneic and orthopneic, slightly obese man who exhibited slight cyanosis, which became more prominent during paroxysms of coughing. He was tachypneic, with a prolonged expiratory phase. The neck veins were distended to a level 4.0 cm. above the clavicles when the patient was raised to 60°. The chest showed a slight increase in the anteroposterior diameter. Fine and medium rales and wheezes were heard over all lung fields but particularly below the scapulas. The heart was believed to be moderately enlarged. There was a regular, rapid rhythm without gallop, and a soft, blowing systolic murmur was heard over the entire precordium. The aortic and pulmonic second sounds were equal. The liver edge was palpable 4.0 cm. below the right costal margin. No other organs or masses were palpable. Pitting edema was present up to the high calf region and was + to ++ over the sacrum. There was no clubbing of the fingers.

The temperature was 99°F., the pulse 120, and the respirations 28. The blood pressure was 110 systolic, 60 diastolic.

Urinalysis revealed a specific gravity of 1.020 and a + test for albumin; occasional hyaline and granular casts were seen in the sediment. Examination of the blood disclosed a hemoglobin of 15.6 gm. per 100 cc. and a white-cell count of 12,000, with 90 per cent neutrophils, 7 per cent lymphocytes and 3 per cent monocytes. The serum chloride was 101 milliequiv., the sodium 134 milliequiv., the potassium 4.5 milliequiv., and the carbon dioxide 32 milliequiv. per liter, and the nonprotein nitrogen 78 mg. per 100 cc., later falling to normal levels. An electrocardiogram taken shortly after admission (and after digitalization) revealed a PR interval of 0.26 second and a QRS interval of 0.09 second. Changes of a slight left-axis deviation were manifested by the standard leads. RSR′ waves were present in Lead V_2. The ST segments sagged in Leads 1, 2, aVL, V_2, V_4, V_5 and V_6. The T waves were low and upright in Leads 1, 2, aVL, aVF, V_2, V_3, V_4, V_5 and V_6. The rate was regular at 104 per minute. A roentgenogram of the chest showed extensive areas of consolidation throughout both lungs, particularly on the left side (Fig. 1)

Upon admission the patient was placed in an oxygen tent, digitalized, sedated and given a mercurial diuretic. Within the ensuing twenty-four hours

there was very slight symptomatic improvement in the face of increasingly apparent physical signs of consolidation or fluid at the left base.

The subsequent course was one of progression of symptoms interspersed with brief periods of improvement. A variety of antibiotics proved ineffective; the white-cell count remained high, reaching 24,000 terminally. Blood cultures were negative, and cytologic studies of the sputum were negative for tumor cells. The course was also complicated by loss of pulsations in the right posterior tibial and dorsalis pedis arteries, with ischemia of the foot although this subsequently cleared. Additional roentgenograms of the chest failed to demonstrate any significant change. Terminally, dyspnea was more severe, and the cough was productive of copious amounts of tenacious, yellowish, occasionally blood-tinged sputum. Rales were more numerous. The patient died on the twentieth hospital day, three hours after a therapeutic bronchoscopy, which revealed no abnormalities except edema and congestion of the mucous membranes and copious secretions.

FIGURE 1. *Roentgenogram of the Chest.*

DIFFERENTIAL DIAGNOSIS

DR. JOHN W. CASS, JR.*: This seventy-six-year-old man had symptoms of cardiac or pulmonary disease of twenty years' duration that during most of this time did not prevent him from doing some sort of work but not his original job. During the final stage of the disease, the last few weeks, he was in myocardial failure that was not responding to the ordinary procedures. It does not seem possible to make a diagnosis of primary heart disease although the duration of the condition and the symptoms could have been on a cardiac basis. Nothing in the history suggests any primary heart disease—no history of rheumatism or any other condition that may have resulted in myocardial failure. The physical examination provided no definite evidence of primary heart disease. The heart was stated to be moderately enlarged. There was a systolic murmur over the entire precordium. The aortic second sound was equal to the pulmonic, which is a little surprising (in this age group one would expect the aortic second sound to be louder than the pulmonic), and I think that the pulmonic second sound was probably actually accentuated. There were minor electrocardiographic changes—a prolonged PR interval and slight left-axis deviation—but not enough for me to make a diagnosis of primary heart disease. Nothing in the laboratory work or course of treatment indicated specific heart disease. Although some type of heart disease must have been present, I am sure it must have been secondary.

There was no evidence that this patient had chronic renal disease. There was an elevated nonprotein nitrogen and carbon dioxide combining power, but in a man of seventy-six who was in cardiac failure and in whom the nonprotein nitrogen is known to have returned to a normal level, that is not sufficient evidence of renal disease.

I believe the heart disease must have been secondary to pulmonary disease. There was a history of pulmonary disease although it was not specific for any particular type. He had progressive cough, dyspnea, sputum and a terminal condition that was apparently complete respiratory failure; it sounds as though he drowned in his own secretions. There was a desperate effort to help him by bronchoscopy, which the physicians would not have done if they had been dealing with definite pulmonary edema on a cardiac basis. The problem of diagnosis boils down to what clues can be obtained from the x-ray films, possibly from sputum studies and probably from biopsy of the lung. I think it is wise to look at the x-ray films now.

DR. STANLEY M. WYMAN: Three examinations were done—the first two, one day apart and the last, ten days after the initial examination. There is an extensive process involving the entire left lung with mottled hazy densities that are not homogeneous (Fig. 1). There is a similar, less pronounced process in the right lung. The heart shadow can be seen only imperfectly on the first two films but fairly well on the third; it is not obviously enlarged; it seems to be within normal limits. The pulmonary vessels cannot be identified individually. There is only a small amount of fluid in the right pleural space; there may be some in the left. The process in the lungs seems

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to be uniform, but the amount of density may be accentuated in the base of the left lung posteriorly.

DR. CASS: Was he fluoroscoped?

DR. WYMAN: No; he probably was too sick to be fluoroscoped.

DR. CASS: There is certainly no cavitation. Both leaves of the diaphragm are quite normal.

DR. WYMAN: Both leaves seem to be in a normal position. There is no obvious cavitation; there are interspersed rarefactions, but I think they are areas of preserved lung. The last two films show a suggestion of some clearing of the process in the right lung; the left lung may be a little less dense than it was originally. This suggests that there is some clearing of an acute process superimposed on something else or of an acute accompanying process, perhaps.

DR. CASS: The x-ray films are very helpful; they immediately rule out certain pulmonary conditions. I am sure from the x-ray films that this man's primary disease was in the lung and that it is unlikely that he had any specific type of heart disease. There are only two facts in the history, other than the long course, that are of help in determining the etiology of the disease. The first is that in 1918 the patient had some sort of pneumonia, which may have been influenza; if so that may have been the start of a chain of repeated infections resulting in a great deal of lung destruction over the years. There was, however, no history of repeated pneumonia; also, the x-ray films do not seem to show any great amount of fibrosis or emphysema. The second helpful fact is that his wife died with a pulmonary illness characterized by cavity formation, which I assume was tuberculosis, so that he had a questionable exposure to tuberculosis. The x-ray films do not definitely suggest tuberculosis, but I cannot rule it out. Tuberculosis in the aged can be entirely a fibrotic disease, and it can be difficult to obtain positive sputum. Those patients die eventually not with the picture of pulmonary sepsis but with pulmonary insufficiency and cardiac failure. On the basis of the history and with the x-ray findings, I cannot make a definite decision about the etiology.

The sputum is the next basis upon which it is possible to make a diagnosis. The description of the sputum is not too helpful. It was an abundant, drowning type of sputum toward the end so it should have been fairly easy with the proper studies to decide whether any type of infection, including tuberculosis, was present. It seems fairly reasonable, therefore, to assume that this was not tuberculosis. The sputum on a single examination contained no tumor cells.

A specific diagnosis of the pulmonary disease may be only academic after the conditions, like tuberculosis, that can be treated specifically are ruled out. To make a definite diagnosis in this case would probably require a biopsy of the lung. Apparently, the diagnosis was brought to a point where treatment was clear and that was all that was necessary. The disease did not respond to antibiotics as it should have done at least temporarily if it had been one of the ordinary infections, excluding tuberculosis. There was no response to cardiac therapy. The pulmonary disease was so far advanced that he had myocardial failure only as a terminal event, and that type of heart disease quite characteristically does not respond to therapy except briefly and temporarily.

By a process of elimination I have chosen a rare, diffuse pulmonary disease such as pulmonary adenomatosis and believe that he died with pulmonary edema in myocardial failure.

DR. RONALD C. SNIFFEN: Apparently, the service had a great deal of trouble treating this man.

A PHYSICIAN: Our reasoning was along the line of Dr. Cass'. The patient's failure to respond to the various measures led us to believe that he had some sort of diffuse pulmonary disease such as adenomatosis.

DR. ALLEN G. BRAILEY: What did Dr. Cass think about embolization?

DR. CASS: I should have mentioned that. I thought it was incidental in a man of seventy-six in a terminal stage.

A PHYSICIAN: Could this have been due to beryllium?

DR. SNIFFEN: Not so far as we know.

DR. CASS: I do not think the x-ray findings or clinical picture are like those seen with beryllium disease.

DR. WYMAN: I had thought of adenomatosis or some bronchogenic tumor as the more likely possibility. I think that Dr. Cass is correct in believing that the patient must have had some superimposed pulmonary edema. I wonder if that copious watery sputum is not a lead in the direction of adenomatosis.

CLINICAL DIAGNOSES

Staphylococcal pneumonitis.
?Alveolar-cell carcinoma.
Chronic pneumonitis.
Arteriosclerotic heart disease.

DR. JOHN W. CASS' DIAGNOSES

Diffuse pulmonary disease, ?adenomatosis.
Pulmonary edema.
Cor pulmonale, with failure.

ANATOMICAL DIAGNOSES

Chronic pneumonitis, type undetermined.
Cor pulmonale.
Hemorrhagic necrosis of adrenal glands.
Thrombosis of popliteal artery, right, and leg veins.
Adenocarcinoma of prostate.

Pathological Discussion

Dr. Sniffen: At the time of death the patient had several incidental findings. There was thrombosis of the right popliteal artery and deep veins of the calf, with early gangrene of the foot. Also, he had a small adenocarcinoma of the prostate.

The heart was not enlarged, weighing 290 gm. However, the right ventricle measured 7 mm. in thickness — a definite cor pulmonale, particularly in the presence of a dilated ventricle. The left ventricle was approximately normal. The lymph nodes of the mediastinum and the bronchial lymph nodes

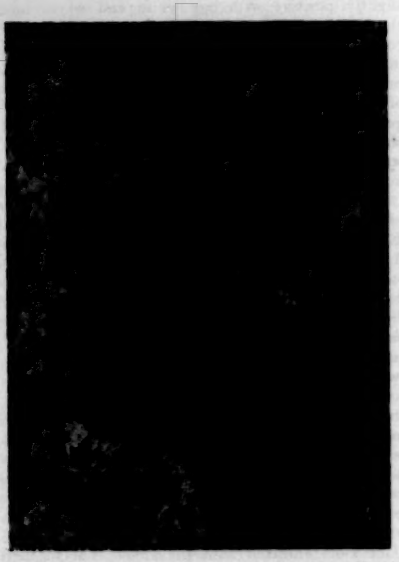

Figure 2. *Photomicrograph of the Lung, Showing Severe Chronic Interstitial Pneumonitis, Lipophages in the Air Spaces and Organization of Exudate in the Alveolar Ducts* (A).

were large but not otherwise remarkable. The right pleural cavity contained 70 cc. of clear fluid and no adhesions; the left side was completely obliterated by adhesions.

The lungs were quite remarkable. Both of them were consolidated and cut like liver. The left lung was more extensively diseased and almost completely consolidated in a rather odd way, in that there were large, firm nodules, which apparently had become confluent. The lesions were grayish, rather glassy and distinctly mucoid. The left lower lobe was completely consolidated but still gave the impression of nodularity. The bronchi were plugged with tenacious yellow exudate, which welled up into the trachea.

The microscopical findings were unusual. There was a chronic bronchitis, with desquamation of the epithelium and infiltration of the wall by lymphocytes and plasma cells and a few neutrophils and eosinophils. The inflammatory process in the parenchyma was largely interstitial (Fig. 2). The walls of the air spaces were thickened, in some areas greatly so, and infiltrated with the same types of inflammatory cells; alveolar epithelialization was prominent. The alveoli were largely obliterated, and the remaining air spaces contained scattered lymphocytes and plasma cells and foci of macrophages. Occasional buds of granulation tissue had grown into the bronchioles and alveolar ducts. In a few areas the parenchyma had lost its architecture, and all that remained was a reticulum infiltrated with inflammatory cells. In an occasional field the process resembled so-called cholesterol pneumonitis in that the reaction was interstitial and was characterized by many foam cells, containing various lipids, cholesterol and cholesterol esters, within the air spaces.

The etiology of the condition is distinctly nebulous. Reports of this type of pneumonia are not infrequent in the literature.[1] The last one that was brought to my attention included a man in his thirties,[2] who showed the same rapid respiratory incapacitation and x-ray picture as this patient. Antibiotics were ineffective and he was intensively studied for bacterial and viral agents without reward; skin tests were negative. He was given ACTH for a week or so, and the lungs cleared remarkably. Then during another week ACTH was gradually discontinued, and the patient was ambulatory around the ward, when suddenly he became severely cyanotic and dyspneic and died within a couple of days, four weeks after the onset. Fienberg,[3] who has reported several similar cases, has tried to link the disease with cholesterol pneumonitis; he has also reported cases in which there were necrotizing granulomas in the lungs and similar granulomas in the kidney. He suggests that the process may be a manifestation of the Arthus phenomenon in the bronchi and that the changes in the parenchyma are secondary to bronchial obstruction. Oddly enough, the patient under discussion had massive hemorrhagic necrosis of both adrenal glands, with thrombi in the capillaries.

References

1. Hamman, L., and Rich, A. R. Acute diffuse interstitial fibrosis of lungs. *Bull. Johns Hopkins Hosp.* 76:177-212, 1944.
2. Schecter, M. M. Diffuse interstitial fibrosis of lungs. *Am. Rev. Tuberc.* 68:607-614, 1953.
3. Fienberg, R. Necrotizing granulomatosis and angiitis of lungs and its relationship to chronic pneumonitis of cholesterol type. *Am. J. Path.* 29:913-932, 1953.

CASE 39522

Presentation of Case

First admission. A four-month-old boy was admitted to the hospital because of an exacerbation of intermittent diarrhea that had been present since the third week of life.

The pregnancy of the mother and the birth of the child had been uneventful. His birth weight was 7 pounds, 14 ounces, and he was sent home on a formula of evaporated milk, 250 cc., water, 250 cc., and Karo, 60 cc., with feedings every three hours. He did well until two weeks of age, when foul-smelling, watery stools were noticed. The formula was altered; however, the diarrhea continued. When, at the age of one month, he was admitted to another hospital, he was placed on a diet of whole boiled skim milk and banana flakes, and the diarrhea lessened. He was sent home to continue on this diet, together with rice cereal and, later, vegetables. He gained weight, but the diarrhea still persisted with about six loose, foul-smelling stools a day. When a vitamin supplement was started, a rash appeared that disappeared when the supplement was withdrawn. At three months of age, the stools had increased to twelve a day. Two weeks before admission, dark blood was seen in a stool, and on the same day two additional stools were described as consisting of red blood alone. The patient was readmitted to the other hospital to be discharged the next day on the same diet but with Bremil (milk preparation) added. One week before admission here he had a running nose, and two days later became hot, and vomited. A physician made the diagnosis of an abscessed ear, and the patient was again admitted to the other hospital, where he was given penicillin and a sulfonamide. He was treated with clyses and improved somewhat, but the diarrhea and vomiting again grew severe, and he was transferred to this hospital.

The mother suffered from hay fever, and a half sister aged nine years was said to be allergic to costume jewelry.

Physical examination showed an alert, well hydrated boy in no apparent distress. The abdomen was slightly protuberant, and tympanitic. The ear drums were not abnormal. The pharynx was minimally injected. A Grade 1 systolic murmur was heard over the aortic area. The scrotum and thighs were edematous from the clyses.

The temperature was 100°F. by rectum, the pulse 90, and the respirations 20.

Urinalysis was negative. The hemoglobin was 10 gm. per 100 cc., and the white-cell count 12,000, with 35 per cent neutrophils, 56 per cent lymphocytes, 5 per cent monocytes, 2 per cent eosinophils and 1 per cent basophils. The white-cell count fell to 8000 on the second hospital day. The serum pH was 7.52, and the carbon dioxide 24 milliequiv., the sodium 144 milliequiv., the potassium 3.1 milliequiv., and the chloride 115 milliequiv. per liter; the total protein was 4.4 gm., the calcium 8.4 mg., and the phosphorus 2.8 mg. per 100 cc. Five days after admission, the total protein was 5.2 gm., the albumin 3.6 gm., and the globulin 1.6 gm. per 100 cc. At this time the alkaline phosphatase was 16.3 units per 100 cc., and cephalin flocculation was + in forty-eight hours. A blood Hinton test was negative. Stools were repeatedly guaiac negative, and were without pus cells. Cultures of the stools were negative for pathogens, as were cultures of the nose, throat and urine. Hollister–Stier skin tests were negative with wheat, beef and egg white and equivocal with cow's milk. Intradermal tests were perhaps slightly positive with egg white and wheat and slightly more positive with cow's milk. An initial roentgenogram of the chest showed an area of increased density in the left lower lobe suggesting pneumonitis, but a later film was clear. A plain film of the abdomen revealed a considerable amount of gas throughout the bowel, but did not suggest obstruction. On an intravenous pyelogram there was prompt excretion of dye on both sides, although intestinal gas obscured detail.

The patient was started on an oral potassium solution with 10 per cent dextrose and water. The diarrhea decreased abruptly, and finally disappeared. A nutramigen formula was started, and was gradually increased to full strength. Boiled cow's milk was gradually substituted, until the patient was discharged on the thirteenth hospital day on whole boiled cow's milk with supplementary feedings of cereal and vegetables. He was having only one or two bowel movements a day.

Second admission (eight days later). He had been well until five days before admission, when he was seen to strain, at which time he passed a stool that was slightly firmer than normal but otherwise not remarkable. Later that day he passed bright-red blood admixed with stool.

Since that time he had had stools twice each day with a large amount of "dark-brownish" blood and black clots admixed with the stool. The mother noticed that the patient had gradually become pale, weak and unusually restless; for the past two days he had appeared pale, sweaty and weak immediately after each bowel movement. On the morning of the day of admission he was seen by the family physician, who found the blood hemoglobin to be 6.4 gm. per 100 cc. Hospitalization was advised.

Physical examination showed a pale, fretful child. There was slight coryza and slight injection of the fauces. On rectal examination the feces were grossly bloody. The examination was otherwise negative.

The temperature was 100.4°F. by rectum, the pulse rate 140, and the respirations 30. The blood pressure was not determined.

The urine had a specific gravity of 1.005 and was normal. The hemoglobin was 4.6 gm. per 100 cc.,

and the white-cell count 26,950, with 37 per cent neutrophils, 60 per cent lymphocytes and 3 per cent monocytes. Two transfusions of 90 and 80 cc. of blood were given at once, after which the hemoglobin rose to 11 gm. per 100 cc. and remained at that level. The white-cell count fell to 12,700. The patient was continued on the Mulsoy (hypoallergenic milk formula) formula and improved. The stools were consistently guaiac positive for the first three hospital days, but then became guaiac negative. At no time were there more than two stools a day. After the transfusions, the bleeding time was six and a half minutes, the clotting time seven and a half minutes, and the prothrombin time 73 per cent. Proctoscopic examination was negative. A plain film of the abdomen and a barium-enema examination were unremarkable.

On the eighth hospital day an operation was performed.

Differential Diagnosis

Dr. Robert M. Todd*: Diarrhea developed shortly after birth, and this infant continued to pass foul-smelling stools for about three months; at that time blood was first noticed in the stool but for only a few days. Then he had a respiratory infection, which responded to antibiotics, but the diarrhea continued and he became dehydrated and was given clyses. At that stage his abdomen was slightly protuberant and tympanitic. After treatment with potassium and glucose solutions the diarrhea ceased, and a week later he passed blood sufficient to reduce the hemoglobin to 4.6 gm. per 100 cc.

With that story I have to consider first infection in the alimentary tract. The protocol states that the stool cultures were negative for pathogens, which I assume were the dysentery and salmonella groups. Other organisms, particularly *Escherichia coli* of the 0.111 and 0.55 groups, have something to do with gastroenteritis in infancy, but in this case I do not think the natural history of the disease favors this diagnosis. Similarly, ulcerative colitis, if we can consider this an infection, is not suggested by the history. There was no history that mucus had been passed, and certainly no tenderness along the course of the colon, which one finds in that disease. From the history it is obvious that a milk allergy was considered, but there was very little to support it. There was no associated urticaria, eczema or asthma, no stool eosinophilia and little evidence from the intradermal tests, although these would not negate the diagnosis. I cannot explain the severe loss of blood on this diagnosis.

Pancreatic fibrosis, another condition that is relatively common in infancy, certainly has to be considered in an infant who passed foul-smelling stools beginning shortly after birth and continuing for some time. But a gain in weight and a sudden cessation of the diarrhea in pancreatic fibrosis are unusual. Furthermore, the stools were not described as fatty. Another point is that the quick recovery from a respiratory infection is very unusual with pancreatic fibrosis. Once these patients get an infection it is extremely difficult for them to get rid of it. There was no record of estimation of the trypsin, either in the duodenal juice or in the stools, which would have helped to exclude this diagnosis. Severe bleeding is not a feature of pancreatic fibrosis, but one could explain some bleeding by a vitamin K deficiency due to faulty absorption of this fat-soluble vitamin.

The blood dyscrasias have to be considered since they can give rise to severe bleeding from the intestinal tract, but usually with this severe type of bleeding with a blood disease there is some evidence of bleeding in other parts of the body such as purpura or ecchymoses. It is possible because of the chronic diarrhea that vitamin C played some part in the bleeding, but I think that in every case of scurvy there are red cells in the urine and examination of the urine in this case was negative.

Hemangioma of the small intestines has been recorded in childhood at a very early age but I do not think that is likely here. In many of the cases with this severity of bleeding there are other hemangiomas, particularly on the skin. With intestinal hemangiomas some mucus might be passed, but not foul-smelling stools, which were recorded. Intestinal polyps may cause bleeding, but usually of a minor degree. About 80 per cent of them are found in the rectum, but in this child proctoscopic examination was negative. Sometimes they are found in the colon and may be observed by barium-enema examination. Again, there were negative radiologic findings, but that does not exclude a polyp. I should say that it would be very unlikely for a polyp to give rise to such severe bleeding.

Intussusception may arise from a polyp or from some other cause. The characteristic feature is recurrent colicky abdominal pain; in the protocol there is no mention of any sort of pain in association with the patient's condition. Moreover, a tumor is palpable in about 8 out of 10 cases, and there was no record of a palpable mass here.

Finally, I come to what I consider the most likely diagnosis, a congenital anomaly of the intestine. Meckel's diverticulum is probably the commonest cause of painless profuse bleeding in this age group, and I should consider that that would be a very adequate explanation for the bleeding that occurred in this child. Probably, there was also some associated malrotation of the intestines and an intermittent obstruction. It is significant, I think, that on one occasion the abdomen was protuberant and tympanitic. Several cases of congenital intestinal anomalies causing chronic diarrhea of the celiac type in young infants have been reported with an abnor-

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mality of the intestine such as a high cecum bound down to the duodenum by so-called Ladd bands; when the bands are divided the celiac symptoms disappear.

I believe in this particular case that a Meckel diverticulum was present with an associated anomaly of development of the small bowel such as a malrotation that could have been responsible for the intestinal symptoms.

A PHYSICIAN: Would you consider duplication?

DR. TODD: I did not specify it in the intestinal abnormalities because I did not have anything to go on, but I think that should be considered.

DR. BENJAMIN CASTLEMAN: Would there be a long history of diarrhea with Meckel's diverticulum alone?

DR. TODD: Unless it was producing some interference with absorption from the bowel, I do not think Meckel's diverticulum would produce the diarrheal symptoms.

DR. NATHAN TALBOT: I wonder if the potassium insufficiency, which may be characterized by either diarrhea or atony of the gastrointestinal tract, would not be a satisfactory explanation for the chronic phase of the diarrhea. Such potassium-insufficiency diarrhea has been produced experimentally in animals. It stops promptly when the potassium deficit is eliminated.

DR. TODD: I think that might explain the late but not the initial diarrhea.

CLINICAL DIAGNOSIS

Meckel's diverticulum.

DR. ROBERT M. TODD'S DIAGNOSES

Meckel's diverticulum.
Malrotation of intestine.

ANATOMICAL DIAGNOSIS

Peptic ulcer in Meckel's diverticulum.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The surgeons, who agreed with Dr. Todd that the probable diagnosis was a Meckel diverticulum, operated on the patient, and found 60 cm. from the ileocecal valve a characteristic Meckel diverticulum, which was resected along with a small portion of the ileum. On gross examination the diverticulum contained an ulceration, which microscopically proved to be of the peptic type, with the characteristic fibrinoid necrosis of the base. As was expected the ulcer was in the small-bowel epithelium, and adjacent to it was gastric epithelium, the source of the hydrochloric acid necessary for the production of the ulcer. It is the peptic nature of the ulcer in the Meckel diverticulum that is strong evidence for the acid theory of the pathogenesis of peptic ulcer.* As far as I know there were no other anomalies; at least the surgeon, who looked carefully, found no other anomalies in the abdomen. The explanation of the diarrhea suggested by Dr. Talbot, potassium insufficiency, is a good possibility. This is borne out by the fact that the diarrhea stopped after potassium was given during the first admission. The diarrhea apparently masked the bleeding at that time.

*Lindau, A., and Wolff, H. Peptic genesis of gastric and duodenal ulcer: especially in light of ulcers in Meckel's diverticulum and postoperative ulcers in jejunum. *Surg., Gynec. & Obst.* 53:421-434, 1931.

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PRESIDENT WESSELL

The institutions under which the three medical schools in Boston are operated each inaugurated new administrative leaders in the recent past. Well served by Dr. Leonard Carmichael during the fifteen years that preceded his call to the Smithsonian Institution, Tufts College, the latest to make a change, brings to its presidential chair Nils Yngve Wessell. On December 9 Dr. Wessell was installed as the seventh president of Tufts College since it established its medical school in 1893. He came to Tufts in 1939 as dean of the College of Liberal Arts and assistant professor of psychology; he became associate professor in 1945 and full professor of psychology in 1947. After 1951 he served the College as vice-president, and was acting president for a few months directly before his present appointment.

The son of a Congregational Minister, President Wessell was born in 1914. He graduated from Lafayette College in 1934 and received the M.S. degree from Brown University in 1935, the Ph.D. degree from the University of Rochester in 1938 and the honorary degree of Doctor of Science from his alma mater in 1951. Trained in psychology, President Wessell has demonstrated a special interest in the clinical activities of his field, having served as resident psychologist at the Bradley Home and Hospital (for neurologic and behavior disorders of children) and as director of the Mobile Child Guidance Clinic at the University of Michigan. Since 1947 he has been consultant in psychology at the Tewksbury State Hospital, the Massachusetts Hospital School and the Lesley-Ellis School. In 1948–1949 he was chairman of the advisory committee of the Veterans Administration Guidance Center at Harvard University. Clinical interest in fields so closely related to the practice of medicine vouchsafe a sympathetic concern with the problems of medical education.

Among the organizations in which Dr. Wessell holds fellowship are the American Psychological Association, Massachusetts Society for Clinical Psychologists, American Association for the Advancement of Science and Sigma Xi and Phi Beta Kappa fraternities. He is also a member of the American Association of Academic Deans, College Entrance Examination Board, Eastern Association of College Deans, American College Personnel Association, Massachusetts Schoolmasters Club, New England Association of Colleges and Secondary Schools and New England Conference on Graduate Education.

In community life President Wessell has served over a widely diversified field, including the following activities: chairman of School and College Group of Greater Boston United War Fund in 1945; chairman of the Institutions Division of the same organization in 1946; member of Speakers Bureau of American Red Cross since 1946; chairman of Massachusetts Colleges Crusade for Freedom in 1951; member of Board of Managers of Middlesex County National Bank; member of Board of Governors of Swedish-American Council of Boston; member of Educational Commission of the National Conference

of Christians and Jews; and trustee of the New England Colleges Fund.

In 1938 President Wessell was married to Marian Sigler, of Kansas City, Missouri. They have a daughter and a son, aged twelve and ten, and have lived on the Tufts campus in Medford since coming to Massachusetts. The *Journal* extends to President Wessell and his College its best wishes for a long and prospering administration of the affairs of one of the leading educational institutions of this region, and particularly of its medical branch and interest.

RETURN OF RIP VAN WINKLE

THE *Journal* of March 19, 1953 contained an article on "Group Practice with Branch Centers in a Rural County" by Dr. Caldwell B. Esselstyn. The paper, which had been presented at a meeting of the Medical Care Section of the American Public Health Association at Cleveland in October, 1952, described the organization and operation of the Rip Van Winkle Clinic, established six and a half years before in Columbia County, New York.

Numerous members of the Columbia County Medical Society took exception to Dr. Esselstyn's paper. In concerted action they despatched a long letter to the editor, signed by no less than twenty-five of their number. This communication, which was published on July 30, indicated that the doctors of Columbia County, and others, disagreed with some of the statements made in Dr. Esselstyn's paper.

Among other things the letter claimed, in regard to the status of the Rip Van Winkle Clinic as a cancer-detection center, that "either through an oversight or through falsification of the application for approval, the American College of Surgeons carried this center on its 'Approval Lists' until the lack of approval of the County Society was called to its attention."

Elsewhere in this issue of the *Journal* a letter may be found from Dr. Paul R. Hawley, director of the American College of Surgeons, denying the allegation regarding oversight or falsification of the application to the College.

Another paragraph in the Columbia County Medical Society letter refers to a young physician in resident training at the Albany Hospital who was alleged to have been discouraged by the dean of the Albany Medical College "from locating in Germantown, presumably at the suggestion of Dr. Esselstyn, whose clinic plans to open a branch there."

Any attempt to influence this physician is specifically denied by Dr. Harold C. Wiggers, dean of the Albany Medical College, in a letter to the editor published in the *Journal* on September 10. A reply to Dr. Wiggers' letter by the physicians of Columbia County appears with Dr. Hawley's letter in the present issue, in company with a pertinent communication from an interested representative of the consumer group, Mr. C. G. Burke, of Ghent, New York.

Further information relating to the Rip Van Winkle Clinic has come to hand in the form of copies of letters approving the Clinic (which is licensed and approved as a dispensary by the Welfare Department of the State of New York) from the director of professional education of the American Cancer Society, Incorporated, the Health Information Foundation of New York, and the commissioner of health of the State of New York.

The *Journal*, having quoted in an editorial in the issue of July 30 the final phrase of the Columbia County physicians' letter of the same date "that *a group has the same responsibility and obligation to maintain medical ethics as does an individual practitioner*," finds that its employment of this axiomatic statement has been misinterpreted to the detriment of the Rip Van Winkle Clinic. The word *group* as used by the *Journal* was not intended to designate the Rip Van Winkle Clinic alone or any other specific organization for the practice of medicine. It may, indeed, be extended to include any aggregation of physicians, however organized, who might fall into the error of overlooking their moral obligations to the community and to their fellow practitioners.

Believing that both sides should be given an equal opportunity of expression where a difference exists, the *Journal* is now of the opinion that no further benefit can be derived from an extension in its columns of the discussion regarding medical practice in Columbia County, New York.

MEASLES ON VIRGIN SOIL

THE extreme contagiousness of measles can seldom be demonstrated these days, for in the ordinary course of events epidemics that make their rounds every other year or so permanently immunize most of the younger members of society.

The effect of measles on a population never previously exposed was demonstrated in the classic description of a pandemic outbreak in the Faroe Islands by Panum, an eyewitness of the great outbreak of 1846. More recently, Christensen and his colleagues reported an outbreak that swept through villages of Southern Greenland in the spring of 1951 after a young sailor, who imported the infection from Copenhagen, visited an infirmary in Julianehab on April 26 during the exanthematous stage of his infection.[1, 2]

The sailor, as sailors will, spent much of his time — and incidentally his most infectious period — roaming widely throughout the port and attended a "dancing-mik" on April 27 (a dancing-mik is presumably a strenuous affair, for within a week or two, 250 persons were down with the virus infection, a fact that gives some idea of potential infectivity in a virgin population). Altogether, 4221 of 4320 residents of Julianehab developed typical infection (giving an astounding attack rate of 97.6 per cent) and of the few who escaped, 31 persons had previously had measles during stays in Denmark.

Several unusual opportunities for the study of the natural history of measles were offered in the course of such a widespread outbreak. For example, all curves of incidence obtained from the larger villages of Greenland showed two large peaks after the source case or cases had been introduced, a fact that is readily understandable if each patient can potentially infect 100 or 200 other persons.

Eighty-three women suffered the disease in the course of pregnancy, mostly in the second half of gestation as far as could be determined (the native Greenland woman does not make special note of her first missed period). In 7 women the infections occurred during the puerperium; of the remaining 76, 26 promptly went into labor and produced 7 abortuses at three to five months, 6 prematurely born infants, of whom 3 died, and 13 infants born at term, of whom 2 died during the first twenty-four hours of life. A phenomenon similar to that which occurs after rubella during the first trimester of pregnancy was not observed: no congenital abnormalities occurred in the infants born of mothers who had contracted measles in early pregnancy. The number of cases is necessarily small, — only about 25, — but the implication is that measles either kills or spares the conceptus.

An interesting observation was made regarding tuberculosis morbidity. By sheer coincidence, a survey for tuberculosis had been completed in the village of Narssak in April just before the measles struck. Resurvey of 352 persons in September revealed 19 new patients with tuberculosis. Previously, 58 patients, 9 of whom had died after measles, had been detected. Thirteen of the 19 new patients showed positive sputums. The investigators had no hesitation in concluding that measles reduces resistance to tuberculosis.

REFERENCES

1. Christensen, P. E., et al. Epidemic of measles in Southern Greenland, 1951. I. Measles in virgin soil. *Acta med. Scandinav.* 144: 313-322, 1953.
2. *Idem.* Epidemic of measles in Southern Greenland, 1951. II. Measles in virgin soil: epidemic proper. *Acta med. Scandinav.* 144: 430-449, 1953.

HANDS ACROSS THE ISTHMUS

THE Pan American Medical Association, no less than hemiglobal in its scope, was founded twenty-six years ago on the principle that "the practice of medicine has no national, racial or religious boundaries." Organized by a group of young physicians studying tropical medicine in New York in 1926, it has grown to an aggregation of 40,000 physicians representing 22 countries of the Americas. Nor is its influence confined to the terrestrial boundaries of these sovereign states; on water as well as on land it works unceasingly in the interests of medical culture.

Its avowed purposes are to promote closer relations among physicians in the countries represented, to develop postgraduate scholarships and to establish postgraduate teaching centers in the various countries of the Association. As a result of these developments three-year rotating scholarships will be awarded annually in such number that, at the end of the first three-year period, 198 physicians will be taking the courses of study, 66 returning each year to their own countries to practice and to teach.

In all, various years having been passed over and the war years having been perforce omitted, 8 Inter-American Medical congresses have been held. The ninth, another ship-to-shore convention, held largely under the aegis of Father Neptune, will convene on shipboard in New York on January 6, 1954, and will sail to conference meeting points in Caracas, San Juan, Ciudad Trujillo, St. Thomas and Havana. Holding brief authority even over Neptune, Dr. Pedro A. Gutiérrez Alfaro, Venezuelan Minister of Public Health and Welfare, the new president of the Association, will occupy the chair.

The newly-graduated Providence Thermometer is nearly ready for sale. Its main peculiarity is that zero represents blood heat.

Boston M. & S. J., *December 28, 1853*

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

PAYZANT—Claude L. Payzant, M.D., of Boston, died on December 5. He was in his sixty-seventh year.

Dr. Payzant received his degree from Boston University School of Medicine in 1910. He was on the staff of the Quincy City Hospital and was formerly president of the New England Physical Therapy Society.

He is survived by his widow and a son.

THORNE — Fred S. Thorne, M.D., of Boston, died on December 6. He was in his sixty-fourth year.

Dr. Thorne received his degree from Harvard Medical School in 1918. He was a member of the staffs of the Massachusetts Eye and Ear Infirmary, Symmes Arlington, Sancta Maria, Newton-Wellesley, Brooks and Carney hospitals, a fellow of the American Medical Association and the American Academy of Ophthalmology and Otolaryngology, and a former vice-president of the New England Ophthalmological Society.

He is survived by his widow and a sister.

MASSACHUSETTS DEPARTMENT OF MENTAL HEALTH

AGING POPULATION AND MENTAL HOSPITALS

Improved health of the population results in a larger number of aging persons and produces a new series of general, medical and sociologic problems. The mental health program to assure adequate coverage of this phase of the total problem must be re-examined.

The plan of management of mental hospitals has been changed by the increasing number of aged patients. These older patients are of two groups: those who grow old in the hospital, and those who are senile when admitted. Most large hospital systems were organized to meet the needs of young schizophrenic patients. The staffing patterns of the institutions were planned to use working squads to do much of the cleaning and maintenance work. The nursing service was set up to provide supervision for these occupational activities, only a few being needed to care for the bed patients. The food services were all set up around the cafeteria system. The bathing facilities were organized along the lines of those in the ordinary Y.M.C.A. or school shower room. The basic purpose of such organization was to provide the maximum amount of care at least possible cost, and with the fewest possible nursing and medical personnel. The need for constructive activity on the part of these patients was recognized and exploited to its fullest to afford the work opportunities mentioned above.

Improved treatment technics have upset the whole system. Almost all the manic-depressive patients who come to the hospital are treated and discharged within thirty to a hundred and twenty days. The variety of modern treatments for schizophrenia have by no means solved the problem, but they do succeed in turning out a large percentage of these patients, and the accumulation rate from schizophrenia is now small. Thus, improvements in treatment have resulted in a difficult economic situation. The older continued-care patients who at one time did a great deal of the simple work around the institution are now becoming too infirm, and former working colonies are gradually being converted into infirmaries to take care of the same patients. The difficulties are compounded. Patients who formerly required no bedside nursing now require such care, and in addition people must be employed to do the menial tasks formerly performed by the patients. This is not a sudden transition, but each year it is necessary to provide more infirmary beds, and supply larger proportions of bedside nursing care. Some hospitals are currently engaged in research projects directed toward chronic patients, principally those with schizophrenia. As these technics improve it is anticipated that still more of the so-called working group will become eligible for discharge to the community, still further compounding the nursing problem mentioned above.

Through the years there has been a gradual change in the types of patients. With improved mental health clinics and outpatient facilities, with a rise in the number of qualified psychiatrists practicing in the community and with an increasing awareness of the management of simple psychiatric problems on the part of the general medical practitioner, a good many of the severely neurotic, mildly depressed and early schizophrenic patients are cared for in the

community and are not referred to state mental hospitals. This is a tremendous step forward in the general health of the community, and one that should be exploited to its fullest. The number of severely disturbed schizophrenic patients seeking institutional care remains amazingly consistent through the years, irrespective of social and economic conditions. As mentioned above, a larger percentage of the newly admitted patients are dismissed. To offset these gains, rates of hospital admission continue to climb, consisting almost exclusively of older patients. In some large mental hospitals, as many as 35 and 40 per cent of the admissions are patients more than sixty years of age. In fact, with the improvement in discharge rates of the younger psychotic patients and in outpatient care both before and after hospitalization, the problem of overcrowding would have been solved medically, rather than structurally, if it had not been for the rise in the number of older patients. These elderly patients can be divided into the following three groups so far as their care is concerned, disregarding the detailed diagnostic criteria.

First, patients who are confused and also physically infirmed. Some have had strokes, and some show generalized weakness and debility. A few die shortly after admission; others may live for two or three years. The care of the physical infirmities of this group has greatly increased the use of consultations, in medicine, surgery and other specialties, and the Department is indeed grateful for the excellent co-operation of local medical groups in handling this phase of the problem.

Secondly, a large group of patients who come to the institution grossly psychotic because of organic disturbances in the brain; in spite of treatment they continue to be disturbed and psychotic. These patients are different from the first group, in that they are physically vigorous, and many of them live for years in the hospitals. Because they are physically vigorous, they adjust themselves reasonably well to general organization and nursing plans, but most of them are unable to work.

Thirdly, another large group of patients who come to the institution extremely confused or disturbed, but who show an improvement in mental symptoms with proper management of diet and correction of physical and dental infirmities. A good many can be returned to the community. The community will accept some of them back, but the families of others lack the resources or the desires to care for them. Some patients are placed in nursing homes and the family care program. A few prefer to stay in the mental hospitals because of the better medical care and the recreational facilities. This seems to be a matter of individual preference of the patient, some of them enjoying the security that they feel in the routine of institutional life. This group of patients is the one often described as "thousands of patients who do not need to be there." These statements are usually based on emotion rather than fact. With adequate supervision in the community many of these patients would get along; without it they would quickly become confused and irascible, and it would be necessary to go through the commitment process again. Improved resources in the community for nursing, recreational and family care, would increase the number of patients who could be dismissed. It should be pointed out, however, that the number of patients involved in this latter group is so small that their removal from the hospitals would not solve the nursing problem.

The majority of elderly patients come in the first two groups. It is obvious that any real solution of the problem will involve prevention, specialized facilities for care at the time of admission, improvement in the community resources and willingness of their families to accept them back after they have improved in the hospital.

These facts may be disconcerting unless viewed in proper historical perspective. An analogous situation that has been worked through involved patients with central-nervous-system syphilis. Forty years ago 10 to 15 per cent of the admissions to public mental hospitals were for some form of syphilis of the nervous system. Most of these patients died within two years of admission. The development of effective treatments for this form of syphilis compounded the difficulties temporarily, because all such patients were given these treatments. Patients with the early form were able to resume their places in the community. Large numbers, however, had the progress of their disease arrested, but did not show sufficient improvement to go back into the community, and stayed in the hospitals for many years. This resulted in an accumulation of chronic patients with syphilis of the brain and added to the nursing difficulties. With further education and emphasis on the early treatment of syphilis, and particularly with the development of the penicillin therapy of syphilis, this problem has been abolished. So few acute cases of syphilis of the nervous system are now encountered that it is difficult to find teaching material of this type. In the management of the problems of aging, medicine has advanced to the point where larger numbers of people are living to an old age, but no effective ways of keeping them in a vigorous productive state of health have been found.

The picture is not entirely negative, however. There are a number of hypotheses, some of which are workable. Some believe that the symptoms of senile dementia can be kept so mild that the person

can adjust himself in the community. All aging persons have periods of confusion, as well as periods when they become irritable and upset. These should be looked upon as normal symptoms of decreased adaptability, or decreased tolerance to frustration, closely akin to diminished cardiac reserve. It is also realized that these older persons cannot tolerate poor diet, toxic processes, loneliness, feelings of defeat and anxiety about their economic and social future. Clinics, such as those of Dr. Robert T. Monroe at the Peter Bent Brigham Hospital, demonstrate that patients who are properly supervised, with attention to these needs and protection from excessive or sudden demands on the part of the environment, can live out their life span without acute psychotic symptoms that make institutional care necessary. Although there is no specific proof, it is believed that persons who are kept constructively occupied show less tendency to deteriorate mentally. There is urgent need for carefully controlled epidemiologic studies in this area. It is hoped that such studies will be carried on here in the Commonwealth, and there is some indication that co-operative efforts will make them feasible. Since one is dealing with an aging organism, it would be fatuous to assume that any effort would totally resolve the problem. However, if 20 per cent of these cases could be prevented, it would be a tremendous boost to the general health and morale of the community, and incidentally would save the Commonwealth thousands of dollars a year in institutional care.

JACK R. EWALT, M.D.
Commissioner

CORRESPONDENCE

MORE ON RIP VAN WINKLE DISPUTE

To the Editor: The *Journal* has published two documents concerning the dispute between the Rip Van Winkle Clinic and certain physicians of Columbia County, New York. The first was a paper, "Group Practice with Branch Centers in a Rural Community," by Dr. Caldwell B. Esselstyn, in the issue of March 19, 1953. The second was a letter, in the issue of July 30, signed by twenty-five physicians of Columbia County. The first stated the purposes, aspirations, practices and history of the Rip Van Winkle Clinic, of which Dr. Esselstyn is medical director, in the city of Hudson in this county, and the second took issue with the first. Both documents are propaganda, as most of the Bible is, in that they try to convince readers of something. I have read both carefully, and several times, and if at the beginning I was certainly unbiased and entirely open to conviction by the more cogent presentment, whichever it might be, the conclusion of my study found me a partisan indeed.

Here are a few of the rhetorical and dialectical stratagems of the twenty-five ethicists in their attack on the Rip Van Winkle Clinic:

Paragraph 6. "Apparently as a subterfuge. . . ." Indictments are not based on "apparently." "Subterfuge" is in semantic distortion. The uncolored word "method" could have been used without affront to justice.

Paragraph 9. Contains a challenge to Dr. Esselstyn's veracity on the allocation of fees to doctors employed by the Clinic. His paper said that these men received a percentage; the letter says that he withheld a percentage from these men. This is remarkable as tautology in reverse, and reminiscent of the disputes of childhood. In view of its origin it is profoundly distressing. This paragraph also contains a boyish innuendo on the length and usefulness of luncheon conferences, and implies something invidious in the departure of doctors from the Clinic. But others not employed by the Clinic have departed this county and seventeen remain with the Clinic — by implication they must be knaves or dupes.

Paragraph 10. Exults that a publicity program sponsored by the American Cancer Society, to have featured the Rip Van Winkle Clinic, was suppressed by the Clinic's professional opponents. This seems hardly beneficial to the county as a whole, and the letter glides in this semantic perversion: "It has also been necessary to block other attempts at advertising." Advertising and publicity are not synonymous; publicity sponsored by an outside organization of austere credentials seems hardly heinous to those of us who fear cancer. The argument advanced by the twenty-five ethicists is censorious not only of the Rip Van Winkle Clinic and the American Cancer Society but also of the Mayo and Lahey clinics.

Paragraph 11. Utilizes "presumably" and "it appears" to establish a case injurious to Dr. Esselstyn. Bluntly, civilized society cannot accept such tactics from her responsible members.

Paragraph 12. "Dr. Esselstyn obviously aims to become the czar of medicine in Columbia County." No evidence is offered of what this means. "Czar" used like this plainly derives from the tabloid newspapers and is undefined and hence valueless. It implies something; what? And cannot twenty-five embattled ethicists prevent the usurpation?

Decidedly the dialectical method pursued by these doctors stifles their case in the fumes of ill feeling. If there is a valid objection to the procedures of the Rip Van Winkle Clinic, they have submerged it beneath a heap of trivia. Their letter has made of me, a neutral layman, a partisan in defense of an institution attacked not for what it is but for what it is insinuated to be.

For certainly this clinic has increased the medical resources of Columbia County. This, to a layman, is the important point. The twenty-five physicians, your correspondents, are pleased at having prevented the establishment of a cancer-detection center at the Clinic. We laymen, the potential beneficiaries, are less delighted at having such facilities halved. We should like to take comfort from a sense of medical adequacy.

Now a personal note to disarm innuendo perhaps to be directed at me. My household has received excellent and devoted medical care from the Clinic and from resident physicians hostile to the Clinic, including some who signed the lamentable letter. My personal physician, a signer, is still my personal physician although I utilize the Clinic for specialized services. This has not injured my health and I should think the interrelation not unhealthy for the profession of medicine in Columbia County. I write this letter voluntarily, without remuneration anywhere or instigation from the doctors in this dismal controversy. It is relevant perhaps to add that I may not be suspected of partiality for Dr. Esselstyn: we have enjoyed a reciprocally cool relation for some years. This cannot affect my wish to see justice done and fair play maintained and my neighbors' health protected.

C. G. BURKE
Ghent, New York

To the Editor: The doctors of Columbia County hesitate to prolong the controversy that appeared in recent issues of the *Journal*. Since Dr. Wiggers has used such terms as "loose and undocumented statement" and "irresponsible and unethical statement" in his letter appearing in the September 10, 1953, issue, a reply seems necessary.

First, we wish to make it clear that it was not our intention to jeopardize either the Albany Medical College or its administrative officer, but to show how one holding high office can be misled by Dr. Esselstyn into action helping his scheme.

The facts are as follows:

Dr. Esselstyn had a conversation with Dr. Wiggers concerning the young physician who planned to practice in Germantown, New York, well after the appearance of local newspaper accounts of Dr. Esselstyn's intentions to open a branch office in Germantown.

The young physician was called to Dr. Wiggers' office for an unsolicited interview.

In spite of the fact that Dr. Wiggers made no attempt to discourage or to encourage the young physician's decision to practice in Germantown, New York, the young physician was discouraged when he left Dr. Wiggers' office. In fact he was so much discouraged that he immediately sought the advice of a high-ranking member of the faculty.

I respectfully request that you publish this letter, which has been subscribed to by Drs. John L. Edwards, Carl G. Whitbeck, Ralph F. Spencer, Lawrence J. Early, Helen M. McEvoy, A. F. McEvoy, Leroy Holbert, Gene S. Rogati, Heinz Salm, Oscar Wilcox, Jr., H. J. Noerling, John Dardess, Leonard M. Niesen, Robert H. Little, Rosewell D. Shaw, Joseph P. Gold, Harold Levine, H. O. Little, A. F. White and R. L. Bowerhan.

HUGH G. HENRY, M.D.

Germantown, New York

To the Editor: In the July 30 issue of the Journal is printed a letter signed by a number of members of the Society of Medicine of Columbia County, New York.

In this letter the following statement is made: "Either through an oversight or through falsification of the application for approval, the American College of Surgeons carried this center (the Rip Van Winkle Clinic) on its 'Approval Lists' until the lack of approval of the County Society was called to its attention."

This statement is not correct. There was no falsification of the application for approval, nor was there any oversight on the part of the American College of Surgeons.

PAUL R. HAWLEY, M.D., *Director*
American College of Surgeons

Chicago, Illinois

PEDICULOSIS CILIORUM

To the Editor: In reference to the paper "Treatment of Pediculosis Ciliorum in an Infant," published in the *Journal* of November 26, may I say that, according to the United States of America Typhus Commission and in our own experience, cases of pediculosis ciliorum in infants are adequately and easily treated by lightly dusting a small amount of 10 per cent D.D.T. powder on the eyelashes of the child when he is asleep?

GEORGE H. FLESSAS, M.D.
Resident, Pediatric Service
Boston City Hospital

Boston

RESTORATION OF LICENSE

To the Editor: At a meeting of the Board of Registration held on October 22, 1953, it was voted that the registration of Dr. Z. Eileen Taylor, 15 Central Street, Winchester, be restored.

ROBERT C. COCHRANE, M.D.
Secretary

State House
Boston

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Man's Back. By Theodore A. Willis, M.D., consulting orthopedic surgeon, United States Public Health Service Hospital, Cleveland, Ohio. 4°, cloth, 161 pp., with 125 illustrations. Springfield, Illinois: Charles C Thomas, 1953. $9.50.

This monograph is devoted to a discussion of the normal and diseased back. The chapters present in order the embryology, anatomy, anomalies, mechanics, and examination, followed by injuries, diseases, tumors, scoliosis, psychoneuroses and malingering, physical therapy and operations. The text is well illustrated; there is a good index, and the publishing is excellent. The book should be in all collections on orthopedics and surgery.

Die neuzeitlichen Brustwand- und Extremitäten-Ableitungen in der Praxis. By Prof. Dr. Herbert Reindell, chief physician, Medizinischen Universitätsklinik Freiburg i. Br.; and Dr. Helmuth Klepzig, assistant, Medizinischen Universitätsklinik Freiburg i. Br. With a foreword by Prof. Dr. Ludwig Heilmeyer, director, Medizinischen Universitätsklinik Freiburg i. Br. Second edition. 8°, cloth, 188 pp., with 70 illustrations. Stuttgart: Georg Thieme, 1953. DM 24.60. (Distributed by Grune and Stratton, New York).

The first edition of this monograph was published in 1951. The author has revised and brought his text up to date. The literature is surveyed and a bibliography of 13 pages is appended to the text. The book should be in collections on electrocardiography.

Emotional Factors in Skin Disease. By Eric Wittkower, M.D., and Brian Russell, M.D. With contributions from Peter Edgell, Desmond Irwin and John Slorach, and with forewords by Dr. R. M. B. Mackenna and Professor D. E. Cameron. 8°, cloth, 214 pp., with 17 tables. New York: Paul B. Hoeber Incorporated, 1953. $4.00. (*A Psychosomatic Medicine Monograph.*)

This composite monograph is the joint work of 5 physicians, who discuss the psychosomatic aspects of diseases of the skin. The text is divided into two parts, general and specific. The general part deals with the psychosomatic approach, development, neuroanatomy and physiology of the skin, and investigation and management of patients. The special part is devoted to abnormal skin sensation and manifestations and psychoses. Lists of references are appended to the chapters and to special diseases, and there is a survey of pertinent literature. There are indexes of authors and subjects, and the publishing is good. The monograph should be in collections on dermatology and nervous and mental diseases.

Essential Urology. By Fletcher H. Colby, M.D., chief, Urological Service, Massachusetts General Hospital, associate clinical professor of genitourinary surgery, Harvard Medical School, and urological consultant, Lakeville Sanatorium, Middleboro, Massachusetts. Second edition. 8°, cloth, 650 pp., with 352 illustrations. Baltimore: Williams and Wilkins, 1953. $8.00.

The first edition of this book was published in 1950 and reprinted twice. The text has been revised and brought up to date. The chapters on diseases of the prostate and testis and on tuberculosis have been thoroughly revised. Lists of references are appended to the chapters, and many new references have been included in this new edition. The book reflects the practice of urology as carried out at the Massachusetts General Hospital. There is a good index, and the publishing is excellent. The book should be in all medical libraries and in the libraries of urologists.

The Use of Drugs: A textbook of pharmacology and therapeutics for nurses. By Walter Modell, M.D., assistant professor, Cornell University Medical College; and Doris J. Place, R.N., instructor in medical nursing, Cornell University New York Hospital School of Nursing. 8°, cloth, 468 pp. New York: Springer Publishing Company, Incorporated, 1953. $4.50.

This new book on drugs, which is intended for nurses, should also be of interest to physicians. The text is divided into 4 parts: the principles of pharmacology; principles of therapeutics; medicine; and materia medica. The third part contains valuable information on medical English and Latin, weights and measures, medical arithmetic and procedures in dosage calculation and the preparation of solutions. The last part, comprising 129 pages, consists of an alphabetical list of drugs of all types, with their descriptions, action and uses, and administration and other information. This is a valuable list that could be used to advantage by the medical librarian as a quick reference source. There is a good index, and the publishing is excellent.

NOTICES

HARVARD MEDICAL SOCIETY

A meeting of the Harvard Medical Society will be held in the main amphitheater of the Peter Bent Brigham Hospital on Tuesday, January 12, at 8 p.m. George W. Thorn will preside. The program will be as follows:

Hydraulic Principles Governing the Circulation in Aortic Valvular Diseases. Richard Gorlin.

Body Composition as Revealed by Isotope Dilution: A status report and a description of the "syndrome of depletion." Francis D. Moore, Isidore S. Edelman, Graham M. Wilson, Caryl Magnus and Margaret R. Ball.

The Effect of Small Hypothalamic Lesions on Compensatory Adrenal Hypertrophy. William F. Ganong and David M. Hume.

Recent Studies of Hyperadrenocorticism: Its pathologic physiology and management. John C. Laidlaw, Hartwell Harrison and George W. Thorn.

Psychiatry in Surgery: A beginning approach in the field of gynecology. Somers H. Sturgis and Doris Menzer.

Cerebral Circulation in Pernicious Anemia. Eugene Robin, Frank H. Gardner, John R. Tyler, C. Sidney Burwell and James Metcalfe.

SOUTH END MEDICAL CLUB

A meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, on Tuesday, January 19, at 12 noon. Dr. R. Adelaide Draper will speak on the subject "Orientation in Postgraduate Medical Education." All physicians are cordially invited.

ROTATING INTERNSHIP, SAINT ELIZABETHS HOSPITAL

The United States Civil Service Commission has announced a new examination for medical officer, to fill the position of rotating intern, at $2800 a year, in Saint Elizabeths Hospital, Washington, D. C. Applications will be accepted by the Executive Secretary, Board of U. S. Civil Service Examiners, Saint Elizabeths Hospital, Washington 20, D. C.

SOCIETY MEETINGS AND CONFERENCES

January 4. New England Cardiovascular Society. Page 1004, issue of December 10.

January 4. American Federation for Clinical Research, Eastern Sectional Meeting. Page 1044, issue of December 17.

January 6, March 3 and April 21. Massachusetts Society for Research in Psychiatry. Page 750, issue of October 29.

January 12. Harvard Medical Society. Page 1087.

January 13. Boston Gastroenterological Society. Page 1044, issue of December 17.

January 19. South End Medical Club. Notice above.

January 22, 23, 29 and 30. International College of Surgeons Regional Meeting. Page 828, issue of November 12.

January 26. Massachusetts Hospital Association. Hotel Statler, Boston.

February 2-4. Examination for Public Health Service Medical Officers. Page 750, issue of October 29.

February 5 and April 9. New England Society of Anesthesiologists. Page 914, issue of November 26.

February 15-20. Pan-American Academy of General Practice. Page 790, issue of November 5.

February 23-25. College of Medical Evangelists Alumni Postgraduate Convention. Page 1044, issue of December 17.

March 15-26. Course in Laboratory Diagnosis of Virus Diseases. Page 1044, issue of December 17.

March 27 and 28. American Psychosomatic Society. Page 1044, issue of December 17.

May 14-16. Fifth Annual International Group of Doctors in Alcoholics Anonymous. Page 1004, issue of December 10.

May 31-June 3. American Urological Association. Page xvii, issue of July 23.

July 22 and 23. International College of Surgeons Regional Meeting. Page 828, issue of November 12.

July 23-29. International Cancer Congress. Page 914, issue of November 26.

September 7-10. Nineteenth Annual Congress of the United States and Canadian Sections of the International College of Surgeons. Page 828, issue of November 12.

September 12-15. Second Interastional Congress of Cardiology. Page 44, issue of July 2.

September 16-18. American Heart Association Annual Scientific Sessions. Page 44, issue of July 2.

District Medical Societies

ESSEX NORTH

January 13. Pentucket Club, 111 Main Street, Haverhill.

May 12. 113th Annual Meeting. Andover Country Club, Andover.

MIDDLESEX EAST

January 20. (Combined with the Auxiliary.)

March 24.

May 11. Annual Meeting. (Harlow Dinner.)

Calendar of Boston District for the Week Beginning Thursday, December 31

THURSDAY, DECEMBER 31

*8:00-8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*9:00-10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.

10:30-11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*11:00 a.m.-12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.

*5:00-6:00 p.m. Surgical Division Meeting. Mount Auburn Hospital, Cambridge.

FRIDAY, JANUARY 1

Holiday.

SATURDAY, JANUARY 2

*8:00-8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*8:30-10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.

*9:00 a.m. Proctology Clinic. Peter Bent Brigham Hospital.

*9:00 a.m. Alcoholism Clinic. Peter Bent Brigham Hospital.

10:30-11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

11:00 a.m.-12:00 m. Blood Clinic. Dr. William Dameshek. Stearns Auditorium, New England Center Hospital.

MONDAY, JANUARY 4

*8:00-8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*8:00-9:00 a.m. Medical and Surgical Clinic on Diabetic Foot Problems. New England Deaconess Hospital.

8:30-9:30 a.m. Clinic by entire Surgical Staff and Anesthesia Staff. Cheever Amphitheater, Dowling Building, Boston City Hospital.

9:00 a.m. American Federation for Clinical Research. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.

10:30-11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

12:00 m. Clinicopathological Conference (Boston Floating Hospital). Pratt Lecture Hall. Joseph H. Pratt Diagnostic Hospital.

*12:15-1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.

7:00-9:00 p.m. Combined Anesthesia Resident Training Program. Jimmy Fund Auditorium, Children's Medical Center, 35 Binney Street.

*8:00 p.m. New England Cardiovascular Society. Morse Auditorium, Museum of Science.

TUESDAY, JANUARY 5

*8:00-8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.

10:30-11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*12:00 m. Pediatric Grand Rounds. Cheever Amphitheater, Dowling Building, Boston City Hospital.

*12:00 m.-1:00 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.

*12:15-1:15 p.m. X-ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.

*12:30-1:30 p.m. Medical Journal Club. Cafeteria, New England Deaconess Hospital.

*4:30-5:30 p.m. Anesthesia Teaching Conference. Stearns Auditorium, New England Center Hospital.

*5:00 p.m. Surgical Journal Review. Mount Auburn Hospital, Cambridge.

*5:00-6:00 p.m. Service Meeting followed by Clinical Conference (Medical, Surgical, Obstetrical), Faulkner Hospital.

WEDNESDAY, JANUARY 6

*8:00-8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

10:30-11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*12:00 m. Boston State Hospital Psychiatric Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.

*12:00 m.-1:00 p.m. Clinicopathological Conference. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.

*12:30 p.m. Weekly Pathological Meeting. Joslin Auditorium, New England Deaconess Hospital.

12:30-1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.

*1:30-2:30 p.m. Pathological Conference. Dr. C. Jones. Nurses' Home, Cambridge City Hospital.

2:00-3:00 p.m. Pediatric Conference for Practitioners. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.

*4:00-5:30 p.m. Fracture Lecture. Boston City Hospital.

*4:00-6:00 p.m. Overholt Thoracic Conference. Joslin Auditorium, New England Deaconess Hospital.

*5:00-6:00 p.m. American Cancer Society Telecast. Diagnosis and Treatment of Uterine Cancer. Dr. Howard C. Taylor, Jr. Children's Cancer Research Center, 35 Binney Street.

*Open to the medical profession.

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VAGOTOMY FOR DUODENAL ULCER*

A Final Survey after Ten Years

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BOSTON

IF one could accept completely the time-honored physiologic concepts of gastric secretion and the equally respected "acid-pepsin" theory of the etiology of peptic ulcer, one would be in a position to eradicate duodenal ulcer by surgical measures. One would control the cephalic phase of secretion very neatly by severing the vagus nerves and manage the digestive or humoral phase of secretion by removing the antrum and pyloric ring. The intestinal phase and any other gastric-stimulating factor would then be controlled by removal of the body and fundus of the stomach, and the upper small bowel. Possibly, adrenalectomy would be advisable for the few unfortunate patients whose steroidal pathways were especially active.

This carries physiologic concepts to absurdity. It leaves the hypothetical patient in an even less enviable position than he was with his ulcer. The treatment would be worse than the disease, and he would be a nutritional and economic cripple. The evident absurdity points up two facts of great importance in ulcer disease: that clinical results, not beauty of rationale, must govern the choice of surgical treatment, and that the search for a nonsecreting upper gastrointestinal tract may be clinically unrewarding.

When the evolution of surgery for peptic ulcer is traced, it is clear that surgeons for fifty years have sought an operation that would be simple to accomplish and would still prevent recurrent ulcer. The early procedures such as pyloroplasty and posterior gastroenterostomy were designed primarily as rerouting procedures to overcome obstruction. Posterior gastroenterostomy, while bathing the upper jejunum in the gastric contents, allowed alkaline duodenal contents to neutralize the acid peptic secretions at the stoma. These operations, although still useful at times, did not prevent recurrence in many patients.

With the advent of subtotal gastrectomy, a definitive attack on the acid-pepsin aspect of ulcer disease was envisaged. The early Bilroth I procedure had as its effect the removal of the antrum and at least some of the acid-bearing portion of the stomach. But it was not enough, and recurrences soon appeared. Subtotal gastrectomy (two thirds of the stomach and all of the antrum) combined with gastroenterostomy seemed to be well conceived. The mortality, initially high, was reduced as surgeons became more adept and as supportive measures and anesthesia improved. The incidence of marginal ulcer, also high in the beginning, became lower (3 or 4 per cent) as surgeons performed more adequate gastrectomies and paid attention to the antrum and pyloric ring. But there were still problems related to subtotal gastrectomy that stimulated an interest in improving the surgery of peptic ulcer.

The result of this interest was vagotomy. In the ten years since its introduction on a large scale, certain definite points have been clarified. Many of these aspects have been brought out by a report of the Subcommittee on Vagotomy of the Committee on Peptic Ulcer.[1] Others have been substantiated by reports by Grimson and his associates,[2-4] Crile, Jones and Davis,[5, 6] Dragstedt et al.,[7, 8] Moore,[9, 10] Brooks and his co-workers,[11] Moore and his associates,[12, 12a-12c] Farmer et al.,[13] Stein and Meyer,[14] Colp and his collaborators,[15, 16] Walters, Belding and Lillie[17] and Glenn.[18]

It is clear that the *mortality* after subtotal gastrectomy is consistently higher (3 to 10 per cent) than that after vagotomy (0 to 3 per cent) or vagotomy and posterior gastroenterostomy (2 to 4 per cent).

It is hard to decide which of the *side effects* are worse. The patient with subtotal gastrectomy may suffer from intestinal and nutritional symptoms. The patient with vagotomy complains of heartburn and fullness after eating, noticeable abdominal pain on occasions, and often a very intractable

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form of diarrhea. Many of these by-products are abated by supplementary posterior gastroenterostomy. Despite these discouraging aspects of ulcer surgery, we again emphasize that poor results are in the minority. Both in this group and in a previously reported group of 175 gastrectomies,[12] the vast majority of patients have been well served by their surgeons.

The efficacy of any surgical procedure for duodenal ulcer depends upon the frequency of *recurrence*. Slight differences in mortality or side effects are obviously important factors to consider, but once stabilized as a procedure that can be carried out with a "reasonable mortality and morbidity," any operation for ulcer must stand on its record of recurrences. This is the essence of ulcer surgery, and this paper reviews a late study of vagotomy in an effort to ascertain if empirical results (as measured by recurrence) justify the continued use of this procedure.

A follow-up analysis of the patients who had vagus resection at the Massachusetts General Hospital between 1943 and 1948 is presented. There were 132 patients in all, most of them having vagotomy in 1946 or 1947. There were a few operations in 1943, and some in 1948. The span of the follow-up period is therefore from six to ten years. This was a group of patients from various walks of life chosen for vagotomy because certain aspects of their disease seemed to make them good candidates. Young patients were sought, particularly males, with high levels of emotional response to their work or surroundings because of the presumed central-nervous-system aspect of their disease. Patients with severe bleeding or obstruction were not considered. The majority had "pure" transthoracic vagotomy because of the firm conviction that only with a normal, intact stomach could the physiologic results of vagotomy be ascertained clinically and studied scientifically.

There was also a group of patients who had had posterior gastroenterostomy and entered the hospital with marginal ulcers. In a few patients gastroenterostomy had been performed at the time of abdominal vagotomy; in a few others vagotomy for marginal ulcer had followed subtotal gastrectomy; finally, there were a few in whom posterior gastroenterostomy was carried out after vagotomy because of obstruction.

Methods of Study

Questionnaire

In the fall of 1952, questionnaires were sent to the 132 patients who had had vagotomy. To date, all but 6 have been heard from (Table 1). Of these 126, almost half had a personal interview, an x-ray examination or a gastric test of secretory function. Some had all three. A questionnaire unsupported by an interview or x-ray examination, may be misleading. The normal optimism of the average man prompts him to belittle his complaints and encourage his surgeon. But close examination of these questionnaires revealed tell-tale discrepancies.* In most cases of recurrence, the patient had professed to symptoms that raised our suspicions. The questions were designed with several purposes in mind:

To disclose patients in whom a suspicion of ulcer existed (they could then be brought to the laboratory for interviews and tests and gastrointestinal x-ray films).

To ascertain, in the large group without ulcer symptoms, how patients were getting along, with special reference to their state of nutrition, diet and abdominal complaints.

To determine what effect vagotomy had had on the type and amount of work each patient could do.

To discover whether these patients were taking medicines or if they had been under a doctor's care for gastrointestinal symptoms.

To find out what the patient thought of his operation.

The vagotomy group as a whole has turned out to be a cohesive one. Frequent return appointments to the gastrointestinal clinics and to doctors' offices, along with a large number of tests from time to time in the postoperative period, prompted them to be "doctor conscious." A large-scale re-evalua-

Table 1. *Details of Ten-Year Follow-up Study after Vagus Resection.*

Type of Operation	No. of Patients	Patients Replying to Questionnaire	Patients Seen in Personal Interview	Patients Given Gastric Tests or X-rays
Vagotomy alone	82	77	33	32
Vagotomy combined with posterior gastroenterostomy	36	35	19	18
Previous gastroenterostomy	20	20		
Simultaneous operation	12	12		
"Late" gastroenterostomy	4	3		
Vagotomy combined with subtotal gastrectomy	14	14	2	2
Totals	132	126	54	52

*An example is the patient who reports that he is fine in every way and well satisfied but who is subsequently found to be taking alkali, Banthine, bentyl and milk and cream frequently for epigastric discomfort.

tion of this same group in 1948[10] emphasized the need for follow-up study and now gives a measure of what time has done to the initial results.

Interview

Fifty-four patients were seen in a personal interview during which searching questions were put to them. These were carried out in some cases in conjunction with x-ray examination or studies of gastric secretion.

X-ray Studies

Forty patients have had gastrointestinal series within the past six to twelve months. These examinations were carried out to search for recurrent ulcer, and to evaluate the changes in gastric motility produced by time.

Gastric Secretory Tests

Twenty-four patients had gastric analyses combined with insulin gastric tests. These studies included free and total acid and determinations of chloride concentration. Twenty-seven patients had studies of uropepsin output.[19]

For several reasons the results of these few tests do not reflect the true status of the group. The number of tests is too small for statistical purposes. It has been shown repeatedly that recurrences of ulcer after surgery do not correlate well with any findings in the laboratory.[20] The finding of a flat insulin gastric test and a negative test for free acid on fasting does not ensure against recurrence. Likewise, a high free acid and rise in acid after insulin is not necessarily indicative of the presence or likelihood of development of an ulcer.

Results

Questionnaires, Interviews and X-ray Examinations

Pure vagotomy (transthoracic). We consider that a patient has an excellent result if he has had no ulcer pain or bleeding, no vomiting and no sensation of severe fullness after meals; if he can eat three regular meals a day; if he has lost no time from work; and if he honestly regards the result as close to perfect.

The result is regarded as satisfactory if the patient has only occasional episodes of abdominal distress (not "ulcer pain"); if he has considerable, but not overwhelming, difficulty with fullness after eating; if he has to watch what he eats; if he has one or two episodes of vomiting a year; if he takes occasional medicines; if he has minor bowel problems; if he has to stay out of work one or two days a year; and if he honestly considers himself free of the ulcer problem but regards the result as not perfect.

There were also a few patients with definite symptoms but without proof of recurrent ulcer, or with symptoms due to the side effects of vagotomy that were troublesome. These two groups are classified as borderline between success and failure, and the results are considered dubious.

The rest are regarded as complete failures because of proved recurrent ulcer, bleeding indicative of ulcer or incapacitating side effects of vagotomy.

Table 2. *Results, Short of Failure, of Vagus Resection after Ten-Year Follow-up Study.*

Operation	Total Patients	Patients with Excellent Results	Patients with Satisfactory Results	Patients with Vagal Symptoms	Patients with Ulcer Symptoms	Patients Who Later Died*
Vagotomy alone	82	31	21	3	6	3
Vagotomy combined with posterior gastroenterostomy	36	17	9	1	1	2
Vagotomy combined with subtotal gastrectomy	14	10	2	1	0	1
Totals	132	58	32	5	7	6

*Not as a result of either ulcer or operation.

In this group of 77 cases (Table 2) the results were classified as excellent in 31, or 40 per cent.* The results in 21, or 27 per cent, were classified as satisfactory.

There were 9 patients in the dubious group. Three had postvagotomy symptoms of a severe degree; 6 had ulcer symptoms but no proof to date of recurrence. Three patients in the pure vagotomy group have died, none of ulcer complications and none of surgical complications.

In 19 patients (25 per cent) the results were classified as failures (Table 3). Three had bleeding, although no ulcer could be shown by gastrointestinal series; 10, or 13 per cent,† had recurrent ulcers. Two had uncontrollable symptoms of obstruction and had a subtotal gastrectomy; in 4 with obstructive symptoms a gastroenterostomy was performed, and these 4 were then incorporated in the group of vagotomy combined with posterior

*A certain number of these patients were interviewed. The results in others were classified as excellent after careful evaluation of their status in the 1948 follow-up study, as well as at the present, so that more often than not, a long-term, frequently repeated evaluation was possible over a period of six to ten years.

†Standard deviation 3.8.

gastroenterostomy. In all, subtotal gastrectomy was carried out after pure vagotomy in 11 cases.

Five patients have not been heard from.

In terms of vagus side effects, these patients have done only moderately well. The vast majority complain of fullness after eating, which reflects the status of gastric motility after vagotomy. For some this compromises daily activities to a considerable degree. In a very few, these symptoms have been almost incapacitating, leading to constant eructation, regurgitation and occasionally vomiting. In a few others, as noted above, these symptoms, particularly when associated with a stenosing duodenal-ulcer scar, have necessitated gastroenterostomy or subtotal gastrectomy. The frequency of postvagotomy diarrhea is now almost nil. One or two patients state that they still have short intermittent episodes of looseness of the bowels, but nothing of any severity. Many have had this complaint, now abated, for two to five years.

The majority of this group have either remained stationary in weight or gained a few pounds. Most patients have continued with their smoking and drinking habits despite strong criticism from the doctor.

Economically speaking, none of the patients in the excellent or satisfactory group have lost time from work. Nor have any been forced to take on easier jobs or shorter hours. Those with results considered failures and some of those with borderline results between failure and satisfactory have lost varying amounts of time from work.

A few patients are still taking medicines. Most of these are in the group of whom we are suspicious of further trouble. Those in the excellent and satisfactory groups on the whole do not resort to medicines for digestive reasons.

It is apparent that the 40 per cent of results classified as excellent and the 27 per cent classified as satisfactory are good from what certainly can be described as the simplest, least traumatizing surgical procedure available today for duodenal ulcer. This in itself is a particularly interesting finding. Our knowledge of the timing of recurrence suggests that most of these 52 patients will continue to do well since they have remained well for six to ten years.

Vagotomy with posterior gastroenterostomy. The present-day acceptance throughout this country of the "failure" of vagotomy alone for the treatment of duodenal ulcer places special importance on the analysis of the results of vagotomy combined with posterior gastroenterostomy. The number of cases is small when compared with those in which vagotomy alone was performed. The group is further divided into 20 patients with previous gastroenterostomy (Table 1), who were admitted to the Massachusetts General Hospital between 1943 and 1948 with marginal ulcers and in whom vagotomy was then performed. There were 12 patients who had vagotomy and gastroenterostomy carried out simultaneously. The grouping is further confused by the addition of 4 patients who had "late" posterior gastroenterostomy to overcome postvagotomy pyloric obstruction. We appreciate the fact that this group lacks uniformity for these reasons and also that patients in whom a marginal ulcer has once developed may not respond to vagotomy in the same manner as those who have had an initial vagotomy with gastroenterostomy. Nevertheless, the fundamental anatomic arrangement is the same in all cases, and our later interpretations are made with this consideration in mind.

TABLE 3. *Data in Patients with Results Regarded as Failures.*

OPERATION	PATIENTS WITH BLEEDING WITHOUT ULCER	PATIENTS WITH VAGAL SYMPTOMS	PATIENTS WITH RECURRENT ULCER	PATIENTS WITH SUBTOTAL GASTRECTOMY	PATIENTS WITH POSTERIOR GASTRO-ENTEROSTOMY (LATE)
Vagotomy alone	3	2	10 (13%)	11	4
Vagotomy combined with posterior gastroenterostomy	2	—	5 (14%)	2	—
Vagotomy combined with subtotal gastrectomy	0	—	1 (7%)	—	—
Totals	5	2	16	13	4

The results were classified as excellent in 17 patients (50 per cent) in this group. In 9 additional patients (25 per cent) results were regarded as satisfactory. Two patients had moderately severe vagal symptoms. One now has ulcer symptoms without x-ray evidence of recurrence. There were no operative deaths. Two patients died of causes unrelated to duodenal ulcer. One patient did not return his questionnaire.

There were 7 failures in the group (20 per cent). Two patients had serious bleeding, with no x-ray proof of ulcer as of this writing. Five patients (14 per cent*) had recurrences proved by operation, pathology specimen or x-ray examination and, in 1 case, by gastroscopy. In 2 cases the recurrence required subtotal gastrectomy. One of the 3 remaining recurrences was controlled fairly well medically, the patient dying from an unrelated cause in 1951. One patient has a large gastric ulcer recurrence at present, and another had a jejunal

*Standard deviation 5.9.

ulcer in 1950 that subsequently healed with medical management.

Vagotomy and subtotal gastrectomy. The present series of cases is small, comprising 14 in which vagotomy was carried out because of marginal ulcer after subtotal gastrectomy. For this reason, perhaps they represent a particularly virulent group in which there is less hope of permanent cure. The results in 13 of these patients can now be classified as excellent. One patient died of unrelated causes, and was found to have a gastric ulcer on the lesser curvature at autopsy.

TABLE 4. *Laboratory Findings in Patients with Recurrent Ulcer.*

PATIENT	PREVIOUS ULCER	OPERATION	YEAR	FASTING FREE HYDROCHLORIC ACID*	INSULIN GASTRIC TEST†	UROPEPSIN	TYPE OF RECURRENT ULCER	YEAR	REMARKS
Ros.	Duodenal	Vagotomy	1946	Low — rise with histamine in 1947; low in 1952.	Slight rise in 1947; flat after 4 hr. in 1952.	—	Duodenal	1951	Recurrent ulcer developed in 1951; subtotal gastrectomy in 1952 for pyloric obstruction.
Mor.	Duodenal	Vagotomy	1947	High normal — rise with histamine in 1949	Flat after 4 hr. in 1949	High	Duodenal	1949	Subtotal gastrectomy in 1949 for active duodenal ulcer
Med.	Marginal	Vagotomy; posterior gastroenterostomy (old).	1946	Low in 1950	Sharp rise in 1947; flat after 4 hr. in 1950	—	Marginal	1950	Subtotal gastrectomy in 1950 for active marginal ulcer
Osb.	Marginal	Vagotomy & posterior gastroenterostomy	1947	Low in 1948	Flat after 4 hr. in 1948	—	Marginal	1948	Marginal ulcer seen at gastroscopy in 1948; patient now well.
Fay.	Marginal	Vagotomy; posterior gastroenterostomy (old).	1947	Low in 1953	Slight rise in 1953	High	Gastric	1953	Patient now under treatment
Pas.	Duodenal	Vagotomy	1947	High in 1953	Sharp rise in 1953	High	Duodenal	1953	Patient now under treatment
Rud.	Duodenal	Vagotomy	1948	High normal in 1950	Not done	—	Duodenal	1950	Subtotal gastrectomy for active duodenal ulcer in 1951
Mora.	Duodenal	Vagotomy	1946	Normal in 1947	1 test flat in 1947; 1 test late rise in 1947.	—	Duodenal	1947	Subtotal gastrectomy for active duodenal ulcer in 1947
Sil.	Gastric	Vagotomy	1946	Low	Flat in 1947; flat in 1948.	—	Gastric	1948	Subtotal gastrectomy for active gastric ulcer
Cha.	Duodenal	Vagotomy	1946	None — rise with histamine in 1952	Not done	—	Pyloric	1952	Subtotal gastrectomy in 1952
Smi.	Duodenal	Vagotomy & posterior gastroenterostomy	1947	Low in 1948	Rise in 1948	—	Marginal	1949	Ulcer pain and hematemesis in 1949; patient died of stroke in 1952.
McN.	Duodenal	Vagotomy	1946	Low in 1949	Rise in 1949	—	Duodenal	1949	Subtotal gastrectomy for ulcer in 1949
Cac.	Marginal	Vagotomy; subtotal gastrectomy (old).	1952	Low in 1952	Flat in 1952	High	Marginal	1952	Recurrent marginal ulcer developed 4 mo. after vagotomy; now healed with medicines.
Eng.	Duodenal	Vagotomy	1944	Normal in 1949	Sharp rise in 1949	—	Duodenal	1949	Subtotal gastrectomy in 1951

*Normal free acid considered to be between 15 and 25 clinical units.

†A positive insulin test is considered to be one in which the fasting free acid rises 20 units or more on stimulation. A positive response in a patient with no fasting free acid is a rise of at least 10 units after stimulation.

X-ray Examination

Gastrointestinal examinations were carried out in most of the cases listed as failures. An additional 40 were performed on patients with results regarded as excellent and satisfactory. When recurrent ulcers have been seen, no clear-cut correlation with gastric motility has been possible. Patients with vagotomy alone revealed old chronic ulcers with scarring, varying amounts of duodenal deformity or pseudodiverticulum formation, and varying amounts of stasis. Those who had had vagotomy with gastroenterostomy now show scarring also, varying amounts of emptying through the pylorus and normally functioning stomas. It can be said, however, that the striking finding in the postvagotomy stomach is a beginning return of motility and tone. Whether this represents a "regeneration" of vagal fibers or an assumption of vagal function by other pathways is an open question.

Tests of Gastric Secretion

In the spring of 1953 we set up a program of study that to date has been carried out on 24 patients with the following aims in sight:

To analyze the basal, fasting free acid, total acid and chloride concentration levels in patients with pure vagotomy. (A few cases of vagotomy combined with posterior gastroenterostomy were included in the study.)

To ascertain the response of the parietal cell and of the gastric chloride concentration to insulin hypoglycemia.

To evaluate the basal uropepsin levels in patients after vagotomy and to evaluate the response of uropepsin to gastric stimulation.*

The tests on the patients who had already had recurrences failed to reflect any consistent pattern so far as basal and stimulated levels of free and total acid are concerned (Table 4). Some showed higher than normal and others quite normal basal acid levels. In some cases a rise of moderate proportions followed insulin hypoglycemia, but none showed the dramatic peak of acid secretion characteristic of the ulcer patient before operation. Others had perfectly flat insulin gastric curves.†

Table 5 shows the results of the tests in the group studied in 1953. The effect of vagotomy was considered successful in most of these patients.

The studies consisted in passage of a Levin tube into the fasting stomach after which determinations of baseline free and total acid and chloride concentration were obtained. Insulin (15 units) was then administered intravenously. Blood samples for sugar determinations were drawn, and gastric samples obtained at half-hour intervals, the tube being clamped between aspirations. Multiposition aspiration was used at the close of each half-hour period to drain the stomach as completely as possible. The aspirations were continued for a total of two and a half hours. We appreciate the inadequacy of simple aspiration in determining the total rate of hydrochloric acid output. We have used the single aspiration only as a guide to free and total acid levels.

Fasting levels of free acid were normal or low (less than 20 clinical units) in the majority of patients with pure vagotomy studied. There were 7 patients in this group who had high levels of free acid (over 20 clinical units) on fasting. One of these was a patient with a recurrent active duodenal ulcer crater. Three were patients who complained of abdominal distress not unlike their old ulcer pain, but whose gastrointestinal x-ray examinations were negative for recurrent ulcer. The remainder had higher than normal levels of fasting free acid, with no clinical or x-ray evidence of ulcer recurrence or other gastric difficulty.

The fasting acid levels in any patient with a gastroenterostomy are notoriously low so that their accurate interpretation is difficult. The patient in this group with a recurrent gastric ulcer had no free acid on fasting.

The response of the normal, intact stomach to insulin hypoglycemia consists of a rise in free and total acid levels beginning about three quarters of an hour after the injection. This rise follows the lowest blood sugar levels by approximately half

TABLE 5. *Laboratory Findings in Patients without Evidence of Recurrent Ulcer.*

PATIENT	PREVIOUS ULCER	OPERATION	YEAR	FASTING FREE HYDROCHLORIC ACID	INSULIN GASTRIC TEST	UROPEPSIN	REMARKS
Lev.	Duodenal	Vagotomy	1946	Normal in 1951	Late rise after 4 hr. in 1951	—	Gastrointestinal series negative for ulcer in 1951 & 1953; ulcer-like pain in 1951; no pain in 1953.
Hei.	Duodenal	Vagotomy	1945	Normal in 1948; high in 1953.	Flat in 1948; flat after 3 hr. in 1953.	High	Symptoms of pyloric obstruction; no ulcer on gastrointestinal series.
Ros.	Duodenal	Vagotomy	1947	Low in 1948	Flat in 1948	High	Patient has heartburn and fullness after eating; x-ray examination negative.
Gal.	Duodenal	Vagotomy	1947	Low in 1947; high in 1953.	Flat in 1947; flat in 1953.	High	No complaints; x-ray examination negative.
Sla.	Marginal	Vagotomy	1945	Low in 1947; low in 1953.	Flat in 1947; late rise in 1953.	High	Patient has had bleeding indicative of recurrent ulcer but no x-ray evidence
Sm., W.	Duodenal	Vagotomy	1946	Normal in 1953	Flat in 1953	High	Patient well; x-ray film normal.
Sea.	Marginal	Vagotomy	1948	Low in 1953	Rise in 1953	Normal	Patient feels very well; x-ray film normal.
Mah.	Duodenal	Vagotomy	1947	Normal in 1953	Flat in 1953	High	Patient well; x-ray examination negative.
Iom.	Duodenal	Vagotomy	1946	Low in 1953	Flat in 1953	—	Patient well; x-ray examination negative.
Jol.	Duodenal	Vagotomy	1946	High normal in 1953	Flat in 1953	High	Patient has recurrent ulcer-like pain, but gastrointestinal series shows no ulcer
Don.	Duodenal	Vagotomy	1945	Low in 1953	Rise in 1953	Normal	Some bleeding; gastrointestinal series negative for ulcer recurrence.
Wal.	Duodenal	Vagotomy	1946	Low in 1953	Rise in 1953	—	Patient well; x-ray examination negative.
Pai.	Duodenal	Vagotomy	1946	Low in 1948; low in 1953.	Flat in 1948; flat in 1953.	High	Patient well; x-ray examination negative.
Mat.	Duodenal	Vagotomy	1947	Low in 1953	Flat in 1953	—	Patient well; x-ray examination negative.
Mar.	Duodenal	Vagotomy	1946	Low in 1951	Flat in 1951	Normal	Patient well; x-ray examination negative.
Cot.	Duodenal	Vagotomy	1946	Low in 1953	Rise in 1953	—	Occasional "ulcer"-like pain; gastrointestinal series negative for ulcer.
Pic.	Duodenal	Vagotomy	1948	Low in 1953	Rise in 1953	—	Patient well; x-ray examination negative.
Sto.	Duodenal	Vagotomy	1947	High in 1953	Rise in 1953	—	Some pain in "ulcer" area; x-ray examination negative.
Hay, A.	Duodenal	Vagotomy	1945	Low in 1948; high in 1952.	Flat in 1948; flat in 1952.	Normal	Patient fairly well; no ulcer symptoms; x-ray examination negative.
McI.	Duodenal	Vagotomy and posterior gastroenterostomy	1947	High in 1950	Flat in 1950	—	Patient well; x-ray examination negative.

*Gray and others showed that the uropepsin in the urine is in fact a direct reflection of the amount of pepsinogen being released in the stomach. In more accurate terms, it has been shown that pepsinogen is absorbed into the blood stream in small amounts before hydrochloric acid has had a chance to activate it. The amount absorbed approximates 1/100th of the pepsin actually produced in the stomach, and the amount in the urine is an exact reflection of change in pepsin production in the stomach. As might be expected, uropepsin levels are high in patients with ulcer disease, and low in patients with gastric carcinoma or pernicious anemia."

†We have seen a variety of combinations. One patient had a recurrent ulcer crater despite a perfectly flat insulin gastric test. Another had a recurrent ulcer with evident continuing hypomotility on x-ray examination. It is of great importance that ulcer recurrence may be observed in the face of a maintenance of the measurable physiologic effect of vagotomy. This leads, of course, to further speculation concerning other etiologic pathways.

an hour. The highest level of acid occurs one to one and a half hours after insulin injection and then slowly returns to normal. The occurrence of "a late response" to hypoglycemia (two to four hours) seen in some of the vagotomy patients has stimulated further thought whether or not pathways other than vagal (? hormonal) are involved.[22]

There was no acid response to insulin hypoglycemia in the majority of cases six to ten years after vagotomy alone. However, 6 patients showed a classic early rise in free and total acid, and 2 a late rise. Of these 8 patients, 1 now has a recurrent duodenal ulcer crater, and 2 have occasional episodes of epigastric "distress" that raise suspicion of activity. The others are symptom free, without evidence of ulcer difficulty. None of these tests lasted longer than two and a half hours so that other late acid rises may have been missed.

The results after insulin in the cases in which vagotomy was combined with posterior gastroenterostomy were varied but impossible to interpret owing to the small number of patients studied. The patient who now has a recurrent gastric ulcer showed a late acid rise after administration of insulin.

TABLE 6. *Gastric Chloride Concentrations before and after Insulin Administration.**

SUBJECT	GASTRIC CHLORIDE CONCENTRATION				
	FASTING	30 MIN. AFTER INSULIN	60 MIN. AFTER INSULIN	90 MIN. AFTER INSULIN	120 MIN. AFTER INSULIN
	milliequiv. / liter	*milliequiv. / liter*	*milliequiv. / liter*	*milliequiv. / liter*	*milliequiv. / liter*
Ma.	83.6	55.0	137.0	137.0	137.2
Sc.	101.2	88.2	124.5	129.8	118.8
Jo.	119.1	105.2	116.9	102.4	112.0
Fa.	108.0	94.6	132.8	138.0	126.7
St.	115.5	108.9	131.6	138.0	126.5
Wa.	126.8	92.4	149.2	154.0	136.5
Pico.	129.1	65.0	123.2	121.0	—
Do.	96.2	92.4	108.8	134.2	140.7
Co.	116.2	85.4	125.7	102.1	92.6
Mar.	103.3	88.6	—	—	100.3
Pa.	117.7	130.4	146.8	134.9	146.8
Io.	100.1	131.4	157.3	126.2	115.5
Sm.	103.1	106.7	100.1	82.8	91.5
Mat.	113.2	116.3	122.8	123.9	104.0
Pi.	100.2	112.4	127.2	—	140.1

*15 units injected intravenously.

The chloride concentration level, although not as important an index of acid secretion as the chloride ion output per unit of time,[11] reflects the level of parietal-cell activity. Chloride concentrations tend to be low in people with achlorhydria and high in patients with active peptic ulcer (the normal range is 85 to 120 milliequiv. per liter).

In the small group of 15 postvagotomy patients studied to date, the fasting chloride concentration levels averaged 108.9 milliequiv. per liter (Table 6). Ten patients showed a drop in chloride concentration half an hour after insulin injection to an average level of 87.6 milliequiv. per liter. The other 5 demonstrated no significant change or a slight rise. For the entire group the average rise, an hour after administration of insulin, was 19.7 milliequiv. per liter.

These data suggest that chloride concentration levels in the postvagotomy stomach are normal but that changes in chloride concentration may occur with stimulation.

The uropepsin data* from urine samples collected over a twelve-hour period are presented in Table 7. The majority fall within the ulcer range (over 1500 units per twelve hours). The average uropepsin output after vagotomy is 2234 units per twelve hours.[19] This is lower than the ulcer mean (3000 units per twelve hours), but higher than normal (<1500 units per twelve hours) and than the mean for patients with subtotal gastrectomy (1400 units per twelve hours).

TABLE 7. *Uropepsin Data.*

SUBJECT	RANGE *units/12 hr.*
Normal person	750–1500
Patient with ulcer	1500–3500
Patient after vagotomy (mean)	2234
Patient after gastrectomy (mean)	1400

DISCUSSION

There appears to be no clear-cut correlation between laboratory findings of gastric secretion and clinical findings of well-being. There may be a complete lack of correlation between acid levels, insulin response and ulcer recurrence. There also appears to be no correlation between low levels of gastric acidity and flat insulin curves, nor between high gastric acidity and rising insulin curves.

However, there does appear to be a trend of change in gastric secretion and function as time passes. Acid levels are higher in more of the patients after vagotomy than they were five years ago; there are more positive insulin tests[1]; there is x-ray evidence of returning gastric motility in more of the patients. Uropepsin levels fail to find their normal range after vagotomy. It appears that pepsin may be more prominent than hydrochloric acid in the production of ulcer. This finding and the trend of secretory levels noted above shed new light on the role of the vagus. Does the vagus control hydrochloric acid secretion to a greater degree than it does pepsin? Does vagotomy in fact effect any radical change in pepsin production? Do the recurrent ulcers represent the end result of "partial escape" from vagotomy and its effect on acid production in addition to an already present substantial level of pepsin? Continued investiga-

*We are indebted to Dr. Seymour J. Gray for the uropepsin determinations done in his laboratory.

tion in the laboratory with patients who have had vagotomy may help to answer these questions.

Although the physiology of gastric secretion and its study are important the final criterion of success or failure in the treatment of an ulcer lies in the clinical evaluation of the patient some time after his definitive surgical procedure.

In 1949 we completed a study of end results in duodenal-ulcer therapy.[12] One of the purposes of that study was to provide a broad background against which other forms of therapy could be viewed in perspective. Reference to these data on subtotal gastrectomy (175 cases) reveals a number of interesting points in comparison with the vagotomy series (vagotomy alone and vagotomy with gastroenterostomy). The mortality, as noted above, was consistently higher after subtotal gastrectomy. In terms of morbidity, recurrent ulcer and the need for subsequent surgery, the data at that time showed that vagotomy failed to hold its own with subtotal gastrectomy.

On the basis of the data presented here it is even clearer that vagotomy alone no longer has a place in the treatment of uncomplicated intractable duodenal ulcer. It has failed primarily because it has not prevented recurrent ulceration and because subtotal gastrectomy has a significantly higher promise of success.

Nevertheless, there is something appealing in the simplicity of section of the vagus nerves, which is capable of curing very intractable ulcer disease in 67 per cent of the patients. Here, then, is an operation with a minimal mortality that can relieve ulcer pain and heal an ulcer crater. The basic defect doubtless lies in our inability to select accurately the patients whose disease is adapted to this approach.

The results in the small series of patients who have had vagotomy combined with gastroenterostomy are disappointing. There have been 5 recurrent ulcers divided between patients who had gastroenterostomy as a separate procedure before vagotomy and those who had gastroenterostomy at the time of or after vagotomy. Patients coming to vagotomy with a pre-existing marginal ulcer may well be classified as a group with virulent ulcer. Whether or not the addition of a much larger number of cases of vagotomy and gastroenterostomy done simultaneously would alter the recurrence rate in this group is hard to say. It seems likely, however, that as time passes, the expected tendency for a marginal ulcer to develop in a patient with a gastroenterostomy will increase, and this will not be counteracted adequately by a concomitant section of the vagus nerves. Gastric digestive function seems to escape the effect of vagus resection as time passes, possibly because other gastric secretory mechanisms go into action. The digestive function is a primitive property and not easily discouraged. Its abnormal activity produces ulcer. Between 1900 and 1935, surgeons learned that when jejunal juice and gastric juice were brought into contact surgically, the stomach too often won out, ulcerating the jejunum rather than yielding to its alkalinizing effect. We find no evidence here that vagotomy will alter that basic relation, though it may postpone the evil day of reckoning.

The results in the small group of patients who have had subtotal gastrectomy followed by vagotomy are of interest. The concept of combining gastrectomy with vagotomy has several advocates.[12, 13] Determination whether or not the magnitude of surgery involved is warranted on the basis of ulcer results must await the passage of time.

Vagotomy has a definite place in the treatment of marginal ulcer occurring after subtotal gastrectomy.

Out of the confusion of the laboratory studies done to date, the following secretory findings appear to be substantiated:

It is possible for a patient to remain free of symptoms and of x-ray evidence of ulcer recurrence for five to ten years despite a positive insulin gastric test and high free acid levels (Table 5).

It is possible for a marginal ulcer to develop in the face of a flat four-hour insulin test and low free acid values (Table 4).

There are patients who still have flat insulin tests eight or nine years after vagotomy.

With the passage of time, the incidence of positive insulin gastric tests is increasing.

With the passage of time, there is a comparable increased incidence of higher free acid values in the fasting samples.

Vagotomy seems to produce only a minor change in uropepsin levels, which remain within the ulcer range eight to ten years after vagotomy.

Summary and Conclusions

Vagotomy alone is not a satisfactory primary surgical procedure for duodenal ulcer when competing with subtotal gastrectomy carried out in competent hands and with a low mortality.

The efficacy of vagotomy combined with posterior gastroenterostomy in the treatment of duodenal ulcer is not supported by our data. Judgment must be reserved because of the high incidence of pre-existent marginal ulcer in our small series. More important, however, is the fact that *recurrent ulcer may occur while physiologic effects of vagotomy persist.* This bodes ill indeed for the patient who has had primary vagotomy combined with gastroenterostomy for duodenal ulcer.

The place of vagotomy in the treatment of marginal ulcer after subtotal gastrectomy is substantiated.

The results of present-day laboratory tests have no consistent correlation with clinical results in the evaluation of surgery for duodenal ulcer.

The patients studied were operated on for the most part at the Massachusetts General Hospital by Dr. Moore and by other surgeons of the staff. We are indebted to the Surgical Service and the Hospital for extensive collaboration in this follow-up study.

References

1. Report of Committee on Surgical Procedures of the National Committee on Peptic Ulcer of the American Gastroenterological Association. *Gastroenterology* **22**:295-499, 1952.
2. Grimson, K. S., Rowe, C. R., Jr., and Taylor, H. M. Results of vagotomy during seven years: clinical observations and tests of gastric secretions. *Ann. Surg.* **128**:621-636, 1952.
3. Lyons, C. K., and Grimson, K. S. Complications following subtotal gastric resections performed since June 1944 for peptic ulcer in 132 patients: comparison with complications following vagotomy in 138 patients. *Surgery* **28**:350-367, 1950.
4. Rowe, C. R., Jr., et al. Early and late effects of vagotomy on gastric secretions and motility. *Surgery* **32**:226-250, 1952.
5. Crile, G., Jr., Jones, T. E., and Davis, J. B. Surgical treatment of duodenal ulcer: comparison of results with and without vagotomy. *Ann. Surg.* **130**:31-37, 1949.
6. Crile, G., Jr. Analysis of vagotomy controversy. *Ann. Surg.* **136**: 752-760, 1952.
7. Dragstedt, L. R., Oberhelman, H. A., Jr., and Woodward, E. R. Physiology of gastric secretion and its relation to ulcer problem. *J. A. M. A.* **147**:1615-1620, 1951.
8. Dragstedt, L. R., and Woodward, E. R. Appraisal of vagotomy for peptic ulcer after seven years. *J. A. M. A.* **148**:795-802, 1951.
9. Moore, F. D. Current practices in surgical treatment of ulcer. *S. Clin. North America* **27**:1071-1087, 1947.
10. *Idem.* Follow-up of vagotomy in duodenal ulcer. *Gastroenterology* **11**:442-452, 1948.
11. Brooks, J. R., Erskine, J. M., Gephart, T., Swaim, O. B., and Moore, F. D. Chloride output rate of human stomach in healthy subjects and ulcer patients: effects of vagotomy and acetylcholine; studies by dye dilution technique. *Surg., Gynec. & Obst.* **90**:155-170, 1950.
12. Moore, F. D., et al. Effect of definitive surgery on duodenal ulcer disease: comparative study of surgical and non-surgical management in 997 cases. *Ann. Surg.* **132**:652-680, 1950.
12a. Moore, F. D., Chapman, W. P., Schulz, M. D., and Jones, C. M. Transdiaphragmatic resection of vagus nerves for peptic ulcer. *New Eng. J. Med.* **234**:241-251, 1946.
12b. Moore, F. D. Etiology of peptic ulcer in light of vagus surgery. *Bull. New Eng. M. Center* **8**:193-200, 1946.
12c. *Idem.* Vagus resection for ulcer: interim evaluation. II. Clinical results. *Ann. Surg.* **126**:664-678, 1947.
13. Farmer, D. A., Horne, C. W., Powell, W. J., and Smithwick, R. H. Effect of various surgical procedures upon acidity of gastric contents of ulcer patients. *Ann. Surg.* **134**:319-331, 1951.
14. Stein, I. F., Jr., and Meyer, K. A. Studies on vagotomy in treatment of peptic ulcer: clinical and physiologic results 3 to 4 years after surgery. *Surg., Gynec. & Obst.* **93**:625-635, 1951.
15. Colp, R. Surgical management of duodenal ulcer. *Surg., Gynec. & Obst.* **91**:306-310, 1950.
16. Druckerman, L. J., Weinstein, V., Klingenstein, P., and Colp, R. Comparative study of subtotal gastrectomy with and without infradiaphragmatic vagotomy in surgical therapy of duodenal ulcer. *Ann. Surg.* **136**:211-216, 1952.
17. Walters, W., Belding, H. H., III, and Lillie, W. I. Physiological and clinical studies of vagotomized patients: study of 331 patients. *Arch. Surg.* **62**:183-205, 1951.
18. Glenn, F. Present status of surgical treatment of peptic ulcer. *J. A. M. A.* **145**:790-794, 1951.
19. Gray, S. J., Ramsay, C., Reifenstein, R. W., and Benson, J. A. Significance of hormonal factors in pathogenesis of peptic ulcer. *Gastroenterology* (in press).
20. Weinstein, V. A., Hollander, F., Lauber, F. U., and Colp, R. Correlation of insulin test studies and clinical results in series of peptic ulcer cases treated by vagotomy. *Gastroenterology* **14**:214-227, 1950.
21. Gray, S. J., Benson, J. A., Reifenstein, R. W., and Spiro, H. M. Chronic stress and peptic ulcer. I. Effect of corticotropin (ACTH) and cortisone on gastric secretion. *J. A. M. A.* **147**:1529-1537, 1951.
22. Porter, R. W., Movius, H. J., and French, J. D. Hypothalamic influences on hydrochloric acid secretion of stomach. *Surgery* **33**: 875-880, 1953.

SURGICAL CARE OF COMPLICATED GASTRIC AND DUODENAL ULCER IN SMALL HOSPITALS*

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THIS report is concerned with the surgical care of gastric and duodenal ulcers in two small hospitals in New Hampshire. It covers a period of two and a half years, ending June 30, 1953, during which gastric resection for gastric, duodenal or gastrojejunal ulcer was performed in 103 cases.

The types of ulcer and primary indications for resection are presented in Table 1. Intractability includes failure of either a gastric or duodenal ulcer to heal on medical therapy, persistent pain or bleeding on a good medical program and repeated perforation.

The circumstances of gastric resection are outlined in Table 2. The word "emergency" is well established in surgical parlance and hospital usage. It is not a good term, psychologically or in lay tradition, and a better one should be found. It too often indicates that an unanticipated, unprepared-for situation is met under conditions of physical stress and emotional tension by whoever is on the scene, and with whatever mediums or equipment happens to be at hand. Emergencies in this meaning probably should never occur in a well run modern hospital, and they are certainly not a tolerable feature in the proper management of massive gastrointestinal hemorrhage. This is not an uncommon disease. The small hospital, as well as the

TABLE 1. *Indications for Gastric Resection for Ulcer.*

INDICATION	CASES OF GASTRIC ULCER	CASES OF DUODENAL ULCER	CASES OF MARGINAL ULCER	TOTALS	PERCENTAGE
Massive hemorrhage	1	11		12	11.7
Bleeding	7	23		30	29.1
Obstruction		10		10	9.7
Intractability	12	35	4	51	49.5
Totals	20 (19.4%)	79 (76.6%)	4 (3.9%)	103	

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large one, should have a plan of action for treating upper gastrointestinal hemorrhage. If rapid therapy is needed, it can then still be methodical and efficient. The immediate operative procedure itself, when required, should be emergency only in the sense that it cannot be scheduled at a chosen time in the future, but the same facilities, co-ordinated teamwork and efficiency should apply as though the operation had been scheduled electively.

The average and median ages for different categories of cases are shown in Table 3. The patients were predominantly of middle age, but 9 (8.7 per cent) were over seventy, and 8 (7.8 per cent) were under thirty years of age. The average age of patients with resection for gastric ulcer was twelve years higher than that of those with duodenal ulcer.

TABLE 3. *Age Distribution in Various Classifications.**

CLASSIFICATION	NO. OF CASES	MEAN AGE	MEDIAN AGE
		yr.	yr.
Elective operation	91	49.6	51.0
Emergency operation	12	51.6	52.0
Duodenal ulcer	79	46.7	46.0
Gastric ulcer	20	58.8	57.5
Marginal ulcer	4	65.8	67.5

*The youngest patient was 25, and the oldest 94 years of age; 8 patients (7.8 per cent) were under 30, and 9 (8.7 per cent) were over 70 years of age.

MASSIVE HEMORRHAGE

Twelve cases, or 11.7 per cent of all operations for ulcer, were emergency procedures. There is an impressive parallelism between duration of symptoms and occurrence of massive hemorrhage (Table 4). Eight, or two thirds of the 12 patients requiring emergency operation, had symptoms of more than three years' duration. Beyond the eighth year, the percentage of emergency cases requiring resection was consistently higher than that of the elective group. However, 1 patient with no previous history had a massive hemorrhage requiring emergency resection; this patient was forty-nine years of age.

Age of Patients

Seven patients (58.3 per cent) with massive hemorrhage were over fifty, and 3 (25 per cent) over seventy years of age (Table 5). The average age of 4 patients requiring emergency operation who had symptoms of less than three years' duration was forty years, 1 being over fifty, and that of 8 patients requiring emergency operation who had symptoms of over three years' duration was fifty-five, 2 being under thirty. Although there were no deaths in this group of 12 emergency resections, one can assume that some chronically ill elderly patients are going to die from massive hemorrhage, even though they have emergency resection to control bleeding and receive the best of modern surgical care. In this small group of cases, it is obvious that patients with symptoms of longest duration who are over fifty years of age (and consequently more often subject to cardiovascular and renal problems) are most likely to present the additional complication of massive, life-endangering hemorrhage.

Five of 12 elective resections in cases with symptoms of less than two years' duration were also done for bleeding as the primary indication. Of the 91 patients with resections under elective circumstances, the indication was bleeding in 30. Preparation in these cases was mainly a matter of restoring blood volume before operation.

In 10 cases the indication for elective surgery was obstruction. There was no emergency resection for obstruction. As is well known, complete obstruction of the gastric outlet that fails to respond temporarily and at least partially to suction and alkalis and rest is probably caused by carcinoma. Acute obstruction from cicatricial contracture, or from edema about an active ulcer, rarely remains complete under therapy, although it may remain functionally intol-

TABLE 2. *Circumstances of Resection.*

TYPE OF PROCEDURE	CASES OF GASTRIC ULCER	CASES OF DUODENAL ULCER	CASES OF MARGINAL ULCER	TOTALS	PERCENTAGE
Emergency	1	11		12	11.7
Elective	19	68	4	91	88.3
	20	79	4	103	

TABLE 4. *Massive Hemorrhage and Duration of Symptoms.*

TYPE OF PROCEDURE	NO. OF CASES	INCIDENCE OF MASSIVE HEMORRHAGE					
		DURATION OF 3 YR.	DURATION OF 8 YR.	DURATION OF 10 YR.	DURATION OF 15 YR.	DURATION OF 20 YR.	DURATION OF 30 YR.
		%	%	%	%	%	%
Emergency	12	66	50	42	25	17	8
Elective	91	36	46	38	17	13	5

erable, and it is in such cases that obstruction is listed as the indication for operation.

Massive hemorrhage from a peptic ulcer requiring emergency gastric resection has been defined in various ways. We have tried to follow the generally accepted definition. As applied in our practice for several years and in this report, massive upper gastrointestinal hemorrhage means blood loss causing the hemoglobin level to fall below 9 gm. per 100 cc., accompanied by alteration in vital signs indicative of shock, and failure to elevate the hemoglobin level and stabilize the vital signs by administration of 1500 to 2000 cc. of blood within a twenty-four-hour period. The average level of hemoglobin on admission in the emergency cases was 7.6 gm., and the highest 9.6 gm., and the lowest 4.6 gm. per 100 cc. (Table 6). The average amount of blood given in these twelve cases from admission to operative control of the bleeding was 3500 cc., the largest amount being 8000 cc. and the smallest 1500 cc.

Hemoglobin level on admission and associated signs of shock are not in themselves indications for emergency resection. In the cases in which elective operations were done, the average hemoglobin reading was 10.5 gm. per 100 cc.; 3 patients had levels below 6 gm., and 12 levels of 9 gm. per 100 cc. or less. The difference is that the bleeding stopped or slowed down so that the hemoglobin level could be raised, the vital signs stabilized, and operation done electively.

Technical Considerations

Judged solely by ability of the pathologist to find the ulcer in the resected specimen, the ulcer was removed in 78 cases (Table 7), including all cases of gastric ulcer. Of the remaining 25, the ulcer was excised from the duodenum in all except 4, which lay in the second portion, on or about the common duct. No effort was made to remove these ulcers; we have tried to leave lesions involving the pancreas from the proximal duodenum in situ, after mobilizing the duodenum, to lessen the risk of pancreatitis. Also, in spite of the fact that a specimen is thereby lost for pathological examination, we have not hesitated to put clamps across and transect through an ulcer in the first portion of the duodenum after mobilization because of the longer duodenal stump thus safely obtained for inversion. So far as we know, duodenal ulcers have no malignant potential.

Seventy-five per cent of the stomach was resected in all cases. Vagotomy was added to the resection for the 4 gastrojejunal ulcers. Gastroenterostomy was of the short-loop retrocolic type in two thirds and of the long-loop antecolic type in one third of the cases.

No emergency resection was done for perforated ulcer nor was any done for obstruction. Massive, otherwise uncontrollable hemorrhage was the only indication for emergency resection.

Table 5. *Age of Patients in Relation to Duration of Symptoms.*

Type of Procedure	No. of Patients	Average Age of Patients with Symptoms for Less than 3 Yr.	Average Age of Patients with Symptoms for More than 3 Yr.	Age over 50 Yr.	Age over 70 Yr.
		yr.	yr.	no. of patients	no. of patients
Emergency	12	40	55	7 (58%)	3 (25%)
Elective	91	58	49	49 (54%)	6 (7%)

Table 6. *Hemoglobin Levels and Amount of Blood Given.*

Type of Operation	Hemoglobin Level on Admission			Amount of Blood Given		
	average gm./100 cc.	highest gm./100 cc.	lowest gm./100 cc.	average cc.	highest cc.	lowest cc.
Emergency	7.6	9.6	4.6	3500	8000	1500
Elective	10.5	—	5.0	—	—	—

Table 7. *Excision of Ulcer in Relation to Pathological Diagnosis.*

Pathological Diagnosis	Removal of Gastric Ulcer	Removal of Duodenal Ulcer	Removal of Marginal Ulcer
	no. of cases	no. of cases	no. of cases
Ulcer in specimen	30	54	4
No ulcer in specimen	—	25	—

The 4 gastrojejunal ulcers, 1 of which was associated with a colic fistula, were resected in one stage. Two resections were done as staged procedures because of severe inflammatory reaction about the duodenum. In no case was a catheter put into the duodenum. We wished that a catheter had been chosen for 1 patient (who subsequently died in uremia), because when the invasive duodenal ulcer was broken into, the base was found to contain the common and pancreatic ducts.

Complications

A number of nonfatal complications occurred (Table 8). The 4 pulmonary infarcts were in the 5 patients who had phlebitis. Elastic support to the legs was used prophylactically in these as in other cases. Treatment after infarction consisted of heparin administration every eight hours, controlled in amount by reference to serially determined blood clotting time (Lee–White method).

Table 8. *Complications.*

Complication	No. of Cases
Auricular fibrillation	1
Thrombophlebitis	5
Pulmonary infarction	4
Coronary thrombosis	1
Prostatic obstruction	1
Prolapsed hemorrhoids	1
Minor wound infection	1
Wound dehiscence	3
Major stomal obstruction	1

One major stomal obstruction occurred, and eventually a new anastomosis was necessary.

Deaths

There were 2 deaths. The first occurred in a fifty-nine-year-old man with a thirty-year history of intractability and bleeding. There had been two previous hospitalizations for bleeding, and one for myocardial infarction. He had cerebral arteriosclerosis and hypertension, and one kidney had previously been removed. At elective operation, the duodenum was too indurated to permit mobilization. The antral mucosa was resected, and the gastric pouch closed. Postoperatively, atelectasis, deep phlebitis and pulmonary infarction developed. Leakage from the gastric stump occurred.

The other patient who died was a seventy-two-year-old man with a thirteen-year history of recurring massive hemorrhages who could not accurately recall the number of previous hospitalizations. Over forty transfusions had been given. Ten years earlier, a posterior gastroenterostomy had been done without benefit. In addition to obstruction, he had large active duodenal and gastrojejunal ulcers. At operation, both ulcers were resected. The duodenal ulcer had eroded about the common duct and pancreatic ducts into the head of the pancreas. A postoperative pancreatic fistula developed. The patient died in uremia on the nineteenth postoperative day.

Discussion

Surgical care in small hospitals should be the equivalent of that in larger institutions. Trained physicians and surgeons, adequate hospital equipment, supplies and facilities are needed. Many towns in New England meet these requirements; others do not.

Our own small hospitals are equipped to make any necessary laboratory tests, including those based on spectophotometry and flame photometry, and service is available around the clock. Each maintains adequate reserves of all standard types of solutions for fluid, electrolyte, protein or blood replacement. There is no question that many physicians can frequently take adequate care of cases of electrolytic imbalance, bleeding or intestinal obstruction by clinical observation combined with intelligent guessing, and the use of only glucose in water and saline solution and blood. However, most patients get along better if the difficult phase of their course is accurately assayed and controlled. An occasional patient is lost without such detailed supervision, regardless of the size of the hospital. In fact, we believe that more lives are lost through minor accidents than through miscarriage of the primary technical procedure. To be sure, if any hospital, large or small, allows surgery to be done that is beyond the capacity of the performer, the anesthetist or the surgical team to handle, catastrophe may be anticipated. Large New England hospitals are often more careful than smaller ones in such respects, but scattered smaller ones are setting standards along these lines of which the most careful of the large might be proud.

The small hospital must be as well equipped and staffed to care for its patient load as the large one is for its greater number of patients, but either succeeds or fails, in terms of the patient himself, largely because of the correctness or incorrectness of care given in the individual case. What solace is found among the living 99 for the wife of the man who dies of a pulmonary embolism ten days after his calf muscles are banged carelessly against a stretcher bar as he is moved from the operating table after a "successful" operation? What has been gained for the patient by a brilliant technical procedure if he is neglected at night and retains pulmonary secretions or inhales regurgitated gastric contents and dies of massive atelectasis? Surgeons as individuals, not the annual census of the institutions in which they practice, control the frequency of these types of carelessness leading to a fatal outcome. Their insistence on vigilance by personnel and administrative provision of properly functioning equipment with which to work, rather than the number of states from which patients were admitted in any

year or the number of names on the hospital payroll, actually determine the outcome for the patient.

Summary

The clinical features of 103 cases of peptic ulcer treated by gastric resection in two small hospitals are outlined. There were 2 deaths. Twelve patients required emergency resection because of massive hemorrhage, and all survived. Principal discussion is devoted to diagnostic and therapeutic measures used in this group of poor-risk, bleeding patients. The problem of gastrointestinal hemorrhage is analyzed, with particular reference to its management in small hospitals.

GASTRECTOMY IN A COMMUNITY HOSPITAL*

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THIS report is an evaluation of the results of gastrectomy in one surgeon's practice in a community hospital (Addison Gilbert Hospital, Gloucester, Massachusetts) since 1946.

Although this procedure is now widely used, and the literature contains many papers on its various aspects,[1-13] no studies regarding its results in community hospitals have been noted. The subject is not static, for mortality and morbidity attend its use and its indications and many technical problems receive wide attention in the published articles.[1-13] In addition, the comparative results of gastrectomy and vagotomy in duodenal ulcer continue to be closely scrutinized.[6,10] It seems highly desirable, therefore, that follow-up studies should be conducted in every hospital where gastrectomy is being done.

At a meeting of Essex South District Medical Society held at the Lynn Hospital in February, 1953, Dr. Francis D. Moore presented some of the findings of the Committee on Surgical Procedures of the National Committee on Peptic Ulcer of the American Gastroenterological Association. Although the results of subtotal gastretomy in duodenal ulcer in the teaching centers were quite uniform (mortality of 2.5 per cent), Dr. Moore had no idea what the results were in the country at large, and he thought the mortality rate might be 10 per cent or higher.

There is a widely held opinion among community surgeons that surgical care in community hospitals and in the centers should not be measured by a double standard. Certainly, one step toward changing such an evaluation is to survey and report results. Colleagues, both in small communities and in the large centers, deserve factual information on surgical activities if these activities are to be judged accurately.

Table 1 outlines the total experience. The average age was fifty-three years, the youngest (a patient with ulcer) being fifteen and the oldest (a patient with cancer) eighty-eight years of age. These patients were unselected and represent all cases in which gastrectomy was considered necessary, regardless of risk. During the same period only 3 gastroenterostomies were performed — all for scar stenosis of the pylorus resulting in complete obstruction.

Duodenal Ulcer

Of 41 patients with duodenal ulcer 35 were males and 6 females, the average ages being forty-six and fifty-one years respectively. The ages ranged from fifteen to seventy-five years. The youngest, a fifteen-year-old boy, had a history of difficulty since childhood. The findings were complete obstruction of the pylorus with a large (2 by 4 cm.) ulcer of the posterior wall penetrating deeply into the pancreas. This patient has been followed for eighty-one months and has remained symptom free and in good health (he went through college on an athletic scholarship).

The average duration of symptoms in the patients with duodenal ulcer was ten years. Indications were intractability in 14 cases, repeated hemorrhage in 8, obstruction in 10, previous gastric surgery and continued pain in 4, gallstones and ulcer pain in 3 and, finally, a question of cancer in 3. The last group represented patients whose ulcers appeared, on x-ray examination, to be situated in the prepyloric area.

Gastric Ulcer

The gastric-ulcer group comprised 15 patients, 8 men and 7 women, with average ages of fifty-five and sixty-two years respectively. The age range was from thirty-five to seventy-three years. The average duration of symptoms was five years. Indications were intractability in 12 cases, hemorrhage in 5 and a question of cancer in all 15. The degree of suspicion of cancer varied in these cases, but in none was the suspicion great. However, a patient in the cancer group was operated on for gastric ulcer, and even at time of operation the ulcer excited no more suspicion of malignant regeneration than that of the average patient in the benign group.

Cancer

This group of patients demonstrated the well known gloomy outlook. Of the 9, resection was performed for palliation in 4 and for cure in 5. During the same period, 7 other patients were explored and

*Presented at the annual meeting of the New England Surgical Society, Watch Hill, Rhode Island, September 12, 1953.
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found to present conditions that offered no hope for palliation. There were 6 men and 3 women, with an average age of sixty-two and seventy-seven years respectively. The ages ranged from thirty-seven to eighty-eight years. Two of the 9 patients underwent total gastrectomy, their ages being thirty-seven and seventy-eight years. The younger died of recurrence in five months. The seventy-eight-year-old patient was well eighteen months after operation. This patient is of interest in that he entered the hospital with complete pyloric obstruction. At operation he was found to have, in addition to the prepyloric tumor causing obstruction, a huge carcinoma of the fundus.

Massive Hemorrhage

The 7 cases in this group represented patients operated on during massive uncontrollable bleeding. There were 6 men and 1 woman, the ages averaging sixty-five years. The oldest patient was eighty-five years. In all these patients blood was rapidly replaced after admission, and surgery was resorted to when the condition of the patient and laboratory studies indicated rapid continued bleeding. An average of 6 units of blood was used before operation, and 2.5 units during and 2.5 units after operation.

The sources of bleeding were gastric ulcer in 2 patients, duodenal ulcer in 2, jejunal ulcer in 2 and gastritis in 1. In all except the last patient a large artery was actively bleeding at operation.

In 1 case, a forty-six-year-old man, who had had a perforated ulcer at twenty years of age and a posterior gastroenterostomy two years later and who had subsequently had repeated episodes of ulcer pain, entered the hospital after a series of tarry stools. Blood replacement was being carried out in the usual manner, when he had a sudden recurrence of rapid bleeding and became unconscious without pulse or blood pressure. Two simultaneous rapid intravenous transfusions were given without effect. No anesthesia was required to open the radial artery, and no bleeding appeared from it when a cannula was inserted. Intra-arterial transfusion was given, and after 200 cc. of blood the patient responded. A systolic blood pressure of 70 was maintained. He successfully underwent subtotal gastrectomy and jejunal anastomosis. In this patient, who was a fisherman with peripheral vascular disease, necrosis of the hand later developed.

Table 1. *Summary of All Cases of Gastrectomy, 1946–1953.*

Indication for Operation	No. of Cases
Duodenal ulcer	41
Gastric ulcer	15
Massive hemorrhage*	7
Cancer	9
Other disease	7
Previous gastric surgery†	10

*Patients operated on during uncontrolled massive hemorrhage.

†Operations included 5 for perforated ulcers, 4 gastroenterostomies and 1 partial gastrectomy 17 yr. earlier.

The small group of 3 cases, listed under "other diseases" in Table 1, comprises 3 patients who were operated on for gallstones. In addition to cholelithiasis, prepyloric tumors were found. Two of these tumors proved histologically to be aberrant pancreatic tissue, and the third was hypertrophy of gastric muscle. The last patient has continued to have symptoms of "bilious vomiting," present for twenty years before operation, in spite of revision of the stoma a year later in another city to which she had moved. The other 2 patients have been well.

Risks

An estimation of risk was made, and 50 patients were considered to be good, 10 fair, and 15 poor risks. There were 11 patients seventy years of age or over, 9 who had severe cardiorenal disease and 7 who were very obese.

Table 2 indicates the lesions found at operation in the 56 patients with duodenal or gastric ulcer. It will be noted that in 49 real pathological findings were encountered.

Table 2. *Lesions Encountered at Operation in 56 Patients.**

Indication for Operation	Patients with Scar	Patients with Ulcer	Patients with Ulcer with Perforation	Patients with Obstruction
Gastric ulcer	0	8	7	0
Duodenal ulcer	7	12	14	8
Totals	7	20	21	8

*Not including patients with massive hemorrhage.

Management

Anesthesia

Continuous spinal and endotracheal anesthesia with oxygen and ether were used in an approximately equal number of patients.

Operation

Table 3 indicates the types of procedure. In all cases, more than 70 per cent of the stomach and the pylorus were removed. In the Billroth I and Hofmeister procedures all the lesser curvature was included in the resection. In the Polya operations nearly all the lesser curvature was removed. In all cases a short loop of jejunum was used for anastomosis, with the distal loop at the greater curvature. The choice of procedure depended on the situation at hand, large size of omentum and omental adhesions in the lower abdomen usually indicating posterior colic anastomosis.

In all but 2 patients with duodenal ulcer, the lesion was removed. Jejunostomy drainage was used in 6 cases. Additional procedures included

jejunojejunal anastomoses in patients who had had previous gastroenterostomies and removal of the greater omentum, spleen and gall bladder. Simple Penrose drains were used when indicated but were never placed directly to a suture line. In an appreciable number of the large ulcers, both duodenal and gastric, that penetrated deeply into the pancreas, copious serous drainage occurred, accompanied, however, by a smooth convalescence in all cases. The greater omentum was removed as well as the mesentery in the 7 most recent cases of gastric ulcer and all patients with gastric cancer operated on for cure.

Inside catgut suture and outside silk on the anastomosis were routine. In wound closure stainless-steel wire suture was most widely used.

An average of 2 units of blood was given during and after operation. All patients were kept on naso-gastric suction until peristalsis became evident. The great majority were ambulatory on the day after surgery. In all cases the lower legs were kept bandaged for five days after operation.

Table 4 gives the immediate results in 75 patients undergoing gastrectomy. The nonfatal complications included mild pulmonary atelectasis, urinary retention and cystitis, uremia, 1 wound infection and 1 case of necrosis of the hand from intra-arterial transfusion. In 1 case empyema of the gall bladder developed from a stone of millet-seed size impacted in the cystic duct.

Early postprandial distress, frequently reported, was rarely noted and was not of sufficient account to justify comment. This group included 3 patients with early and transient diarrhea and 3 with occasional regurgitation of bile for several weeks. Two patients had mild occasional dumping syndrome, which in 1 patient has disappeared entirely and in the other is represented by a full feeling that is no longer annoying and occurs less than once a month.

There were 4 postoperative hospital deaths, in 3 of which post-mortem examination was performed.

Deaths

The first patient was a fifty-six-year-old man who was operated on during uncontrollable massive hemorrhage. He had had duodenal ulcer for years as reported by his physician and radiologist. At operation, hypertrophic gastritis was found, and subtotal gastrectomy was done, with a good immediate response. Six days after operation, paroxysmal tachycardia, recurrent hemorrhage and cardiac decompensation occurred and were followed by death. At autopsy no bleeding point was found, only gastritis and normal postoperative surgical findings being apparent.

Another patient, an eighty-eight-year-old woman, had constant pain and vomiting caused by pyloric obstruction from carcinoma. She lived for ten days after resection, dying in coma. There was no evidence of surgical difficulty. Permission for autopsy was not obtained. The cause of death was cerebral thrombosis.

In a seventy-year-old obese man, complete pyloric obstruction followed a penetrating duodenal ulcer. After operation atelectasis and leakage from the duodenal stump developed; drainage was performed, and he recovered from this procedure and was ambulatory, with normal gastrointestinal function. A pulmonary embolism occurred 28 days after operation. Autopsy demonstrated the pulmonary

Table 3. *Types of Procedure.*

Procedure	Patients with Duodenal Ulcer	Patients with Gastric Ulcer	Patients with Massive Hemorrhage	Patients with Cancer	Patients with Other Diseases	Totals
Hofmeister anterior colic resection	17	1	1	2		21
Hofmeister posterior colic resection	7	2	0	0		9
Polya anterior colic resection	9	0	3	1	1	14
Polya posterior colic resection	8	3	2	1	2	16
Billroth I resection	0	9	0	3	0	12
Total gastrectomy	0	0	0	2	0	2
Additional procedure	8	9	3	5	3	28
Drain	17	9	4	4	3	37

Table 4. *Immediate Results in 75 Patients.*

Average Postoperative Hospital Stay	Average Duration of Postoperative Gastric Suction	Average Degree of Postoperative Temperature Rise	No. of Patients with Elevated Temperature* for 2 Days	No. of Patients with Nonfatal Complications	No. of Deaths	No. of Autopsies
days	*days*	*°F.*				
15.7	2.8	1.6	7	11	4	3

*To 100.6°F.

embolus as well as local inflammation about the stump.

The last of these patients was a sixty-four-year-old man with a high, fixed nonprotein nitrogen (77 mg. per 100 cc.) In addition to coronary sclerosis he had prepyloric ulcer, a question of cancer and uncontrollable pain and vomiting. After resection he lived for twenty-eight days, dying of uremia. At autopsy chronic nephritis, pleuritis, pericarditis and normal surgical findings were observed.

TABLE 5. *Follow-up Data in 59 Patients with Ulcer.*

DATUM	No. OF CASES
Symptoms:	
Ulcer pain	0
Hemorrhage	1*
Gastrointestinal symptoms	1†
Alcoholism	6
Hernia	2
Weight‡:	
Loss of average of 18 pounds	32
Gain of average of 13 pounds	15
No change	10
Subjective result:	
Working activity not limited	57
Patient well satisfied	53
Patient satisfied	6
Evaluation:	
Excellent	45
Good	12
Fair	2

*Silent hemorrhage, in an alcoholic patient with a negative x-ray examination.

†Alcoholic patient.

‡The average loss for the entire group was 6 pounds.

FOLLOW-UP DATA

Table 5 gives the follow-up results of the 59 surviving patients who were operated on for gastric and duodenal ulcer, including those with massive hemorrhage. (One patient of the 6 who survived massive hemorrhage subsequently died of cancer.) had a duodenal ulcer with obstruction and penetration into the gall bladder. In another alcoholic patient serious hepatitis has developed.

Four patients have had surgical procedures since gastrectomy; 1 for small-bowel obstruction in the pelvis from a previous gynecologic operation, and another for bowel obstruction from an adhesion just distal to the stoma. A patient with empyema of the gall bladder required drainage. The fourth patient was recently operated on for gangrenous appendix.

Patients were requested to state their opinion of the results of their surgical treatment and indicate whether well satisfied, satisfied or dissatisfied. It will be noted that none were dissatisfied, and 53 were well satisfied.

Table 6 gives the follow-up data of the patients operated on for gastric cancer.

Table 7 shows results of the Billroth I procedure in 12 patients operated on for gastric lesions. Seven of the 12 patients had radical subtotal gastrectomies including the greater omentum and the mesenteries, as well as the first portion of the duodenum.

TABLE 6. *Follow-up Data in 9 Patients with Cancer.*

DATUM	No. OF CASES	
Death from recurrence*	3	Average 8 months
Death from other causes	2	
Postoperative death	1	
Patient living and well	3†	

†One (65 yr. of age) for 12 mo., in excellent health, with 10-lb. weight gain; another (78 yr. old) for 18 mo. after total gastrectomy, well, with weight gain; and 1 (80 yr. of age) for 34 mo., well except for slight cerebral accident.

The gastric stump was prepared by the Hofmeister method; the Furniss clamp was used along the lesser curvature, all of which was removed. In all cases as much stomach was resected as if a Hofmeister modification of a Billroth II procedure had been used. This operation requires the presence of a normal duodenum. The average time required for operation in the entire group of 75 patients was a hundred and sixty-one minutes. In the 12 patients undergoing Billroth I gastrectomy, the average time required was a hundred and fifteen minutes.

TABLE 7. *Results of Billroth I Procedure in 12 Patients with Gastric Lesions.**

OPERATION FOR GASTRIC ULCER	OPERATION FOR GASTRIC CANCER	RADICAL RESECTION	AVERAGE POST-OPERATIVE HOSPITAL STAY	AVERAGE TEMPERATURE RISE	MORBIDITY	AVERAGE WEIGHT GAIN	PATIENT'S OPINION OF RESULT	RESULT EVALUATED EXCELLENT	RESULT EVALUATED GOOD
NO. OF CASES	NO. OF CASES	NO. OF CASES	*days*	*°F.*		*lb.*		NO. OF CASES	NO. OF CASES
9	3	7	14	1.4	0	5	Well satisfied	11	1

*Average age 60 yr.; oldest patient 80 yr. of age.

The follow-up study ranged from four to eighty-one months. The average was twenty-eight and seven-tenths, and the mean twenty-three months.

Alcoholism has been an occasional problem in that patients with alcoholic tendencies operated on for severe ulcer have subsequently been able to drink alcoholic beverages without real difficulty. One patient, a profound alcoholic, has recurrent diarrhea and vomiting; x-ray studies remain completely negative. Surgery was mandatory, for she

Summary

The results of gastrectomy since 1946 in 75 patients in a community hospital are reported. The average follow-up period was twenty-eight and seventenths months. There were 4 hospital deaths, with autopsies in 3. At the time of this report the results in 57 of the 59 patients with ulcer are considered to be good or excellent, and those in 2 are fair. The patients' own estimates indicate that 53 are well satisfied, 6 satisfied, and none dissatisfied.

In 12 patients with gastric lesions, a Billroth I procedure required a shorter operative time and yielded excellent results.

The survey of this small group of cases shows results reasonably similar to those reported from the large medical centers.

References

1. Borden, A. M. Radical gastrectomy for benign gastric ulcer. *Surg., Gynec. & Obst.* 97:151-158, 1953.
2. Colp, R. Surgical management of duodenal ulcer. *Surg., Gynec. & Obst.* 91:306-310, 1950.
3. Pollard, H. M., Bolt, R. J., Ransom, H. K., and Orebaugh, J. E. Results of surgical treatment of duodenal ulcer: comparison of vagotomy and subtotal gastrectomy five years postoperatively. *J. A. M. A.* 150:1476-1479, 1952.
4. Stewart, J. D., Hale, H. W., Jr., and Hix, J. E. Gastric resection for peptic ulcer in poor-risk patients. *New York State J. Med.* 49: 2911-2914, 1949.
5. Welch, C. E., and Allen, A. W. Gastric ulcer: study of Massachusetts General Hospital cases during ten-year period 1938-1947. *New Eng. J. Med.* 240:277-283, 1949.
6. Stevens, G. A., Kipen, C. S., and Ross, W. L. Comparative concurrent results of vagotomy procedures, conventional gastric resection and hemigastrectomy with subtotal vagotomy. *California Med.* 73:229-231, 1950.
7. McNeer, G., VandenBerg, H., Jr., Doan, F. Y., and Bowden, L. Critical evaluation of subtotal gastrectomy for cure of cancer of stomach. *Ann. Surg.* 134:2-7, 1951.
8. Ross, F. P., and Warren, R. Safeguards in gastric resection for duodenal ulcer. *New Eng. J. Med.* 248:475-481, 1951.
9. MacLean, L. D., Hamilton, W., and Murphy, T. O. Evaluation of segmental gastric resection for treatment of peptic ulcer. *Surgery* 34:227-237, 1953.
10. Report of Committee on Surgical Procedures of the National Committee on Peptic Ulcer of the American Gastroenterological Association. *Gastroenterology* 22:295-499, 1952.
11. Hoerr, S. O. Management of bleeding from upper gastrointestinal tract. *New Eng. J. Med.* 248:404-408, 1953.
12. Allen, A. W., and Welch, C. E. Subtotal gastrectomy for duodenal ulcer. *Ann. Surg.* 136:688-707, 1946.
13. Palmer, W. L., Kirsner, J. B., and Levin, E. Internist views surgical treatment of peptic ulcer. *J. A. M. A.* 146:1041-1044, 1951.

MUCOSAL HYPERTROPHY OF THE STOMACH*

Report of a Case

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THE clinician and the roentgenologist are confronted periodically with the management of a patient in whom large gastric rugal folds have been found. The differential diagnosis must include mucosal spread of an anaplastic carcinoma, lymphoma, hypertrophic gastritis and mucosal hypertrophy, with the possible inclusion of a chronic inflammatory granuloma, such as sarcoid or syphilis.

Mucosal hypertrophy of the stomach has been variously termed Menetrier's disease[1] (*polyadénome en nappe*) and tumoral hypertrophy,[2] and is often mistakenly called chronic hypertrophic gastritis and diffuse gastric polyposis.[3] It is uncommon, and its natural history unknown. The changes that take place in the gastric mucosa have no anatomic similarity to chronic hypertrophic gastritis or gastric polyposis, nor is there any reason to believe that the condition is a forerunner to malignant change. Mucosal hypertrophy is characterized by true thickening of the gastric mucosa, resulting from elongation of the otherwise normal glands. The giant rugae thus formed were likened to cerebral convolutions in Menetrier's description of the disease in 1888. The mucosal thickening cannot be ascribed to inflammatory infiltration and edema, for there is no increase in the usual complement of interstitial cells within the membrane.

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Case Report§

A 58-year-old candy salesman entered the Worcester Memorial Hospital with the diagnosis of a "stomach tumor." Six months previously nausea and vomiting had first developed, either during a meal or immediately afterward, particularly when he had eaten quickly. Vomiting relieved the nausea. There was no associated dysphagia, hematemesis, epigastric distress, melena, change in bowel habits or weight loss. One month before admission, during a routine annual checkup at another hospital, a "tumor" of the stomach was noted on x-ray study, and gastroscopic examination showed hypertrophied gastric rugae without mucosal ulceration. A biopsy was reported as "acute gastritis." The gastric aspirate was stated to contain no free hydrochloric acid, and only "a few units" of combined hydrochloric acid. A Papanicolaou smear of the gastric aspirate was reported as negative.

Physical examination revealed a healthy-appearing and well nourished man. The only positive physical finding was a large, nontender, movable mass in the left upper quadrant of the abdomen. The blood pressure was 150/75.

The temperature, pulse and respirations were normal.

Urinalysis was negative. The hemoglobin was 12.9 gm., and the white-cell count 3550, with 78 lymphocytes, 20 neutrophils and 2 eosinophils. The total serum protein was 5.34 gm. per 100 cc., with an albumin of 4.3 and a globulin of 1.04 gm. per 100 cc. The fasting blood sugar and nonprotein nitrogen were normal. A guaiac test on the stools was negative. A gastrointestinal series suggested greatly enlarged rugal folds, with filling defects in the upper third of the stomach (Fig. 1). Although repeat cytologic examination of the gastric aspirate was negative for tumor cells, it was believed that a malignant tumor could not be ruled out without operation.

Through a thoracoabdominal approach total gastrectomy and splenectomy were performed, followed by an anastomosis between the esophagus and duodenum. Recovery was uneventful.

The stomach was very large, measuring 17.5 cm. along the lesser and 48 cm. along the greater curvature. Externally, it was not abnormal apart from dilatation of the veins along the lesser

§We are indebted to Paul Ware, M.D., for permission to publish his case.

curvature. The rugal folds throughout the cardia, fundus and body of the stomach were greatly hypertrophied, pale pink and glistening. The folds ran longitudinally to the prepyloric area,

FIGURE 1. *Detail View of the Barium-Filled Stomach at the Level of the Gastric Angle, Showing Greatly Thickened Rugal Folds.*

where the mucosa became flat and grossly normal. The large convolutions in the fresh state averaged 2 cm. in width and 2 cm. in height (Fig. 2). The musculature averaged 3 mm. in

FIGURE 2. *Cross-Sectional Comparison of a Normal Stomach (below) with the Stomach in Giant Mucosal Hypertrophy (Fixed Specimens).*

thickness. The serosa appeared normal. The regional lymph nodes were not enlarged, and the spleen was not remarkable.

Microscopically, the gastric glands were greatly increased in height but were not tortuous and had a normal configuration. The individual cells appeared normal. In some areas small cysts had formed, usually at the base of the elongated glands but occasionally in the mid-zone (Fig. 3). Mitotic activity in the neck zone of the glands was not excessive. In a few areas herniation of the glands through the muscularis mucosae had

FIGURE 3. *Low-Power Photomicrograph, Showing the Extreme Elongation of the Normally Configurated Mucosal Glands except for Occasional Cyst Formation.*
There is no increase in inflammatory cells.

occurred. Intestinal metaplasia of the gastric epithelium was not found.

DISCUSSION

The practical clinical importance of mucosal hypertrophy of the stomach lies in its recognition

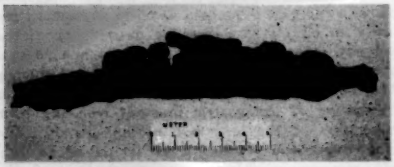

FIGURE 4. *Cross Section of the Stomach in a Case of Multiple Polyposis (Fixed Specimen).*
The patient, a fifty-eight-year-old man had had mild epigastric fullness and distress for two months. He was well fifteen years after operation. Note the individual polyps.

and differentiation from hypertrophic gastritis, malignant tumor and diffuse polyposis (Fig. 4). The last condition is characterized by clusters of

closely placed polyps, either sessile or pedunculated, but all with separate mucosal attachments. Microscopically, the glands are elongated and tortuous, and the cells may be atypical. Dolan and Sherman[3] recently reviewed the subject of mucosal hypertrophy and collected 26 cases, including the one they reported. With justification, they stressed the necessity of distinguishing mucosal hypertrophy from chronic hypertrophic gastritis.

In a review of the reported cases it is obvious that the symptoms of this gastric change are not impressive. Often, there is a history of epigastric or upper abdominal discomfort without a relation to food. Ingestion may relieve or aggravate the discomfort. In addition, there may be anorexia, eructation, nausea and vomiting. Some patients have lost weight, have been anemic and have complained of lethargy, headaches, constipation or diarrhea. There are no pertinent physical findings.

The roentgenologist is faced with a difficult problem, since mucosal hypertrophy may mimic infiltrating carcinoma and lymphoma; furthermore, the giant folds cannot be obliterated by pressure on the stomach. The gastroscopist can visualize the large rugae that show no ulceration, and here again, the folds do not recede with inflation of the stomach. Still one cannot be certain that malignant infiltration is not present. A biopsy through the gastroscope is encouraging in a negative sense.

Helpful laboratory findings have not been recorded. In the gastric juice the free hydrochloric acid may be normal or diminished; according to Dolan and Sherman[3] there is a tendency to hypochlorhydria. Blood in the gastric aspirate and stool is unusual. Balfour et al.[4] have discussed the occurrence of hypoproteinemia in association with giant hypertrophy of the gastric rugae. Their patient suffered from severe hypoproteinemia, which was not relieved by medical measures but was restored to normal after total gastrectomy.

The finding of a neutropenia with a relative lymphocytosis in the case reported above may have been an error, since the determinations were not repeated. This observation has not been recorded in the condition by others.

From the standpoint of anatomy this case appears to differ in no way from that usually described. Typically, the stomach shows an unaltered serosa, apart from dilatation of the blood vessels. The wall is not stiffened, and the mucosa in a large area, or diffusely, exhibits enormous, hyperemic, freely movable rugae like cerebral convolutions that are often covered by an excessive mucous secretion. Microscopically, there is elongation of the gastric glands, with retention of the normal pattern and cellular detail. There may be marked intestinal metaplasia, microscopic cyst formation and herniation of the glands through the muscularis mucosae. There is no increase in the inflammatory-cell population of the mucosa. There is no real indication that the condition precedes cancer, although Matzner, Raab and Spear[5] reported a case of anaplastic cancer developing ten years after the discovery of benign giant gastric rugae in a fifty-year-old man.

Summary and Conclusions

A case of mucosal hypertrophy of the stomach, a rare but distinct condition characterized by the formation of giant rugal folds made up of elongated glands of normal configuration and differentiation, is reported. There is no apparent relation to gastritis, and peptic ulceration does not occur. Its practical importance lies in the necessity for differentiation from anaplastic carcinoma, lymphoma and multiple polyposis, which may produce the same roentgenologic and gastroscopic appearance. Hypoproteinemia and achlorhydria may occur. There is no evidence that this is a precancerous condition.

References

1. Menetrier, P. Des polyadénomes gastriques et de leurs rapports avec le cancer de l'estomac. *Arch. de physiol. norm. et path.* 4 s. 1:32-55 and 236-262, 1888.
2. Dolan, P. T., and Sherman, P. H. Tumoral hypertrophy of gastric mucosa: case report and summary findings. *Am. J. Digest. Dis.* 19:171-175, 1952.
3. Brunn, H., and Pearl, F. L. Diffuse gastric polyposis: adenopapillomatosis gastrica. *Surg., Gynec. & Obst.* 43:559-598, 1926.
4. Balfour, D. C., Jr., Hightower, N. C., Jr., Gambill, E. E., Waugh, J. M., and Dockerty, M. B. Giant hypertrophy of gastric rugae (Menetrier's disease) associated with severe hypoproteinemia relieved only by total gastrectomy: report of case. *Gastroenterology* 16:773-781, 1950.
5. Matzner, M. J., Raab, A. P., and Spear, P. W. Benign giant gastric rugae complicated by submucosal gastric carcinoma. *Gastroenterology* 18:296-302, 1951.

MEDICAL PROGRESS

HYPERTENSION IN PREGNANCY

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IN discussions of hypertension in pregnancy the term "toxemias of pregnancy" has been discarded. Pre-eclamptic toxemia is the only potentially toxic syndrome, and even that has not been established. Hypertensive disease in pregnancy is classified in three groups, as follows: essential hypertension (patients with pre-existing vascular disease); renal disease (patients with pre-existing renal disease, with or without hypertension); and pre-eclamptic toxemia and eclampsia. It is believed that a superimposed pre-eclamptic toxemia is likely to occur in the first two groups. It is difficult to prove the development of a superimposed lesion on a pre-existing one, but because the early effects of pre-eclamptic toxemia are primarily renal and vascular, it is only reasonable to assume that a previously damaged renal or vascular system predisposes to the development of pre-eclampsia. However, it may take months or years of careful follow-up study to make a definite diagnosis and it is often impossible, clinically, to classify individual cases.

To understand properly the problem of hypertensive disease in pregnancy, one must first comprehend certain physiologic alterations in the normal pregnant woman. The most important of these in relation to hypertension is the effect of pregnancy on the water and electrolyte metabolism. Dieckmann[1] has shown that there is a delayed excretion of water and sodium in the normal pregnant woman. Why this is so is not clearly understood. The possibility of the presence of the antidiuretic hormone of the pituitary gland in abnormal amounts or a change in adrenal physiology particularly involving desoxycorticosterone has been considered. However, the basic clinical fact that pregnant women store water and sodium is well established.

About 60 per cent of all pregnant women have edema of some type. The dependent edema of the legs is largely mechanical in origin owing to increased venous pressure. This is a common clinical finding and is of no particular importance in relation to the development of hypertension. Generalized edema of the face, hands and abdominal wall is of much more significance. This is not mechanical in origin and definitely indicates fluid retention. The most serious form of water and sodium retention is the fluid held in the extravascular spaces of the various tissues and organs. Normally about 35 per cent of the body fluid is stored in these spaces, and much more can be stored there. In addition, there may be a marked increase in intracellular fluid and displacement of cellular potassium by sodium. This tissue storage of fluid is most significant in relation to the development of pre-eclampsia. Frequently, there is no visible edema even when large amounts of fluid are retained. Rapid and excessive weight gain is the only clinical evidence of the retention of this fluid. Rapid and excessive weight gain in the pregnant woman is primarily fluid retention.

The fluid retention is due to sodium retention. Lack of proper sodium excretion by the kidneys and excess sodium intake in the diet are the primary causes. It is well to remember that the sodium intake in the diet of the average woman is considerably in excess of what she can efficiently eliminate in the pregnant state.

Another important physiologic and clinical disturbance in pregnancy is the increased load on renal function. Pregnancy is about the best clinical test of kidney reserve. There are many women who have sufficient kidney function for the normal nonpregnant state but whose kidney reserve has been damaged by previous renal disease. In the nonpregnant state, no tests are sufficiently delicate to demonstrate the kidney lesion. Yet with the added load of pregnancy definite signs of renal failure may well develop. Just what causes the added load and strain in the kidney in pregnancy is not well understood. Changes in adrenal function, the excretion of large amounts of steroids, various metabolic changes of pregnancy, increased blood volume and cardiac work, and fetal metabolism may be involved. The fact remains that a normal pregnancy may be too great a load for a kidney with a low reserve.

RENAL DISEASE

Renal disease in pregnancy is one of the most serious complications and one that offers great difficulty in diagnosis and treatment. With the definite presence of this disease, the prognosis for both mother and baby is much worse than in either essential hypertension or pre-eclamptic toxemia. Severe chronic nephritis causes lowered fertility. One does not see many such patients who have become pregnant. A more frequent problem is the early chronic nephritis with kidneys that still function reasonably well in the nonpregnant state.

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From a clinical point of view, it is frequently impossible to make a differential diagnosis between different types of chronic renal damage. The most common type appears to be chronic pyelonephritis; many patients with this form of disease have had acute pyelonephritis in childhood, with residual renal damage and lowering of kidney reserve. Frequently, the diagnosis was not established at the time of the acute episode. Therefore, there may be no past history of the disease (although a past history is of great value, its absence by no means rules out the condition). Patients may have a sufficient kidney reserve to enable them to live in good health in the nonpregnant state. The addition of the load of pregnancy may bring on the first signs and symptoms. If a patient is seen first in the last trimester of pregnancy, the differentiation from pre-eclamptic toxemia may be most difficult. However, with repeated pregnancies, signs of renal damage tend to appear earlier and become more severe. This appearance in repeated pregnancies with increasing severity is in direct contrast to pre-eclampsia, which does not tend to be present in successive pregnancies or become successively more severe.

Certain specific problems are more acute in renal disease than in other hypertensive states. The first is that each pregnancy causes further injury to an already damaged kidney. The life expectancy of the patient is shortened by each pregnancy. Signs of renal failure appear earlier and become more acute. Therefore the first pregnancy of such a woman offers the best chance for a healthy living child; with each succeeding pregnancy, the prognosis for child and mother becomes poorer. Every effort should be aimed at a successful conclusion to the first attempt.

In addition to the danger to the mother, the established diagnosis of chronic renal disease offers a less than 50 per cent prognosis for survival of the child. The fetus frequently dies in utero during the last month, or else the infant does not survive labor or does not have sufficient vitality to survive after birth. Although the placenta does not tend to separate in chronic nephritis as it does in acute pre-eclampsia, there is a marked tendency to infarction of the placenta. Why this is so is not understood, but the typical placenta in chronic nephritis is small and contains many white and yellow infarcts. This is in contrast with the placenta of pre-eclampsia, in which acute hemorrhagic (dark-red) infarcts tend to form. The infarcts in chronic nephritis are a gradual rather than an acute formation. Frequently, a third of the placenta is infarcted; this is the limit of safety for the baby's survival. In cases of death in utero, half or more of the placenta may be infarcted; because of lack of proper nutrition, the fetus tends to be small for its stage of uterine maturity.

The diagnosis of the milder forms of chronic nephritis offers great difficulty. Any patient who shows albumin or casts in the urine during the first half of pregnancy must be considered as a possible case of chronic nephritis. These patients may or may not have an accompanying hypertension. Renal-function tests should be done, particularly to demonstrate the patient's ability to concentrate the urine; a fixed or limited specific gravity is definite proof of this condition and gives a poor prognosis. Other tests are of little value in milder cases. A rise in nonprotein nitrogen or other changes in blood chemistry are rarely found in the mild case. An established hypertension, in addition to the urinary findings, makes the prognosis much worse. The established severe nephritis, with changes in renal-function tests, signs of early renal failure and hypertension, means a very poor prognosis. Eye-ground changes may be of diagnostic importance.

The treatment of chronic nephritis in pregnancy consists primarily in avoidance of excessive weight gain and of fluid and electrolyte retention and in sufficient rest. A high-protein diet is indicated to avoid hypoproteinemia from loss of albumin and the accompanying development of edema. A low-sodium intake is probably the most important factor in diet. With already damaged kidneys, the retention of sodium and water becomes a greater problem than in the normal pregnant woman. Any excessive retention of fluid tends to precipitate renal failure. Therefore, weight gain must be kept at a minimum.

It is most important that the patient be carefully watched and examined at frequent intervals. A few days or a week may bring about a serious change in her condition. Edema or weight gain, increase in albuminuria and hypertension are all signs of impending trouble. Visual disturbances and headaches are of prognostic significance. As long as there is no change in the general clinical picture the patient may be safely carried on until the fetus becomes sufficiently mature for survival.

In many cases, usually in the last trimester, sudden signs of renal failure develop with fluid retention and increase in weight, followed by increase in albumin and casts in the urine, occasionally with red blood cells in the sediment and a rise in hypertension, especially affecting the diastolic pressure. There may also be a rise in nonprotein nitrogen, indicating the development of a pre-eclamptic toxemia superimposed on an already damaged kidney (most authorities believe this to be so although it is difficult to prove). Certainly, a developing toxemia is more rapid and virulent in the presence of renal disease than in a patient with normal kidneys. The combination of toxemia with renal failure is a most critical state. At the earliest signs of renal failure, the pregnancy must be terminated for the sake of both the mother and the

baby; the former may go into irreversible renal failure, and the latter may die in utero.

In the patient whose status is unchanged up to the last month, termination of pregnancy must be seriously considered. Even if there is no sign of impending renal failure, there are definite indications for delivery. The last month of pregnancy may cause serious and permanent damage to the kidney, since this is the time when renal failure is most likely to occur. The sooner the load is taken off the kidney, the less chance of serious damage. It is also during the last month that the fetus is most likely to die in utero. Increasing placental infarction, in addition to any toxemia, may have a serious effect on the baby. If it does not die in utero its vitality may be so lowered as to make it unable to survive birth. The whole situation must be carefully considered, and the optimum time for delivery chosen.

The method of delivery depends on the individual case. In a multipara with the vertex engaged and a soft and partly dilated cervix, induction of labor by rupture of the membranes may be the procedure of choice. In most primiparas cesarean section is indicated. In the critically ill patient, one must weigh the risk of abdominal surgery and accompanying shock against the frequent difficulty of induction from below.

The patient with very mild nephritis and no signs of toxemia or increasing renal or vascular damage during the pregnancy and with no hypertension may be safely allowed to go to term and be delivered by spontaneous labor.

Essential Hypertension

Essential hypertension is believed to be primarily due to vascular disease involving spasm of the arterioles. Of unknown etiology, it resembles pre-eclamptic toxemia in many ways and yet is a distinct entity. In the early stages no kidney damage can be demonstrated, and its presence in pregnancy is a much less severe complication than that of renal disease. In its advanced stages when kidney damage can be demonstrated, it responds to pregnancy as any other type of renal disease.

Frequently, pregnancy is the precipitating factor in latent and potential hypertension, occurring during the first pregnancy in many young women with no previous history of hypertension. Once this condition has developed, it tends to remain after termination of the pregnancy. In a patient with essential hypertension appearing for the first time during pregnancy pre-eclamptic toxemia may be thought to be developing, but in these early cases there rarely is albuminuria or signs of kidney damage.

Other young women have a pre-existent essential hypertension that is apparent before the onset of pregnancy; if the condition is mild, the prognosis for the pregnancy is good. The few patients who have malignant hypertension before pregnancy constitute a dangerous and critical group.

The clinical diagnosis of essential hypertension in pregnancy is made from the pre-existence or the appearance of hypertension early in pregnancy. With negative urinary findings and no signs of kidney disease, the diagnosis is made by exclusion.

The classification is important because a patient with mild essential hypertension has a much better prognosis than one with chronic renal disease. Although all authorities do not agree, it is my opinion that essential hypertension is unaffected by pregnancy unless a superimposed pre-eclamptic toxemia develops. With an already damaged vascular system and arteriolar spasm and possible arteriolar constriction, the patient already has the vascular picture of pre-eclampsia. Therefore, it is clear (and this is substantiated clinically) that these patients have a greater tendency to pre-eclamptic toxemia than those with a normal vascular system. However, most of these patients, under proper care, pass through pregnancy — and many through several pregnancies — without any temporary or permanent change in the hypertension.

This by no means indicates that this group should be treated casually; they must be under strict care and supervision. Any rise in blood pressure or development of albuminuria warns of impending pre-eclampsia. This does not usually occur until the last trimester. Such signs should be regarded with the utmost seriousness because if pre-eclampsia develops the toxemia is likely to be more severe and rapid than that in the patient with a normal vascular system. Termination of pregnancy is indicated as soon as true pre-eclampsia develops.

The treatment of essential hypertension in pregnancy is to direct all endeavor to the prevention of the development of pre-eclamptic toxemia. This, again, is largely dependent on the prevention of water and electrolyte retention. The patient should be on an extremely low-sodium intake. This diet must be carefully explained and given to the patient on a printed sheet. She must be warned of the danger of her condition, and it must be explained that any departure from her instructions may cause serious trouble. Her weight must be carefully checked at least once a week during the second half of pregnancy. The development of any edema or excessive weight gain (2 pounds a week or 5 pounds a month) must be regarded as fluid retention, and the patient as being in the earliest stage of pre-eclampsia. Hospitalization is the treatment of choice, although in exceptional circumstances the patient may be treated at home under close supervision for a week. A serious attempt must be made to produce a diuresis. All possible sodium must be eliminated; ammonium chloride may be given, and the patient kept at complete bed rest. It is at this stage of fluid retention that pre-eclamptic toxemia may be prevented. Once albuminuria and an increase in hypertension

have occurred an irreversible stage of the disease has developed. With clinical signs of pre-eclampsia, either mild or severe, the disease will be present until the termination of pregnancy.

If on treatment at home or in the hospital a marked diuresis has been accomplished within a week, the prognosis remains fairly good. A good response to dehydration consists of a weight loss of 8 to 15 pounds. A check of fluid intake and output is of help but is difficult especially in hot weather, when fluid loss through the skin and lungs may be excessive. Weight loss is the best and simplest guide to the patient's progress.

The question of free or restricted fluids during the period of diuresis has been much debated. The conclusion appears to be that the elimination of sodium is the important factor and that possibly free fluid aids in flushing out the sodium.

For the patient who does not respond to attempts at diuresis by losing weight or even continues to gain, hospitalization is necessary. Albumin shortly appears in the urine, and the blood pressure begins to rise; the patient has reached the stage of true pre-eclampsia and must be treated as such. With the progress of the disease, termination of pregnancy is soon indicated. As in chronic nephritis, the type of delivery depends on the individual case. Those favorable for induction and delivery from below should be treated in this manner. In those unfavorable for this procedure, a cesarean section may be the method of choice.

Women who have passed uneventfully through a pregnancy complicated by essential hypertension are usually unharmed by the pregnancy. In these cases, further pregnancies are relatively safe unless there has been some exacerbation of the disease. On the other hand, patients with the more severe types, especially those complicated by pre-eclampsia, should be warned against frequent and repeated pregnancies.

Pre-eclamptic Toxemia

Pre-eclamptic toxemia is a hypertensive state appearing usually in the last trimester and disappearing shortly after the termination of pregnancy. As mentioned above, it may be superimposed on previously existing renal vascular damage. This disease is most common in young primiparas although it also appears in older multiparas. Pre-eclampsia has no great tendency to reappear in subsequent pregnancies. The patient who has recurring hypertension with increasing severity in succeeding pregnancies probably has some underlying renal or vascular disease.

Certain abnormalities of the pregnancy state tend to increase the incidence of pre-eclampsia. Among these are twin pregnancies, hydramnios, overlarge babies and hydatidiform mole. These conditions have in common an overdistention of the uterus.

The etiology of pre-eclampsia is unknown. Many theories have been propounded, but they have not stood the test of time. The most commonly accepted assumption at present is that because of some interference with the uterine circulation, anoxemia of relative severity develops in the placental area. Owing to this anoxemia there is a breakdown of certain toxic substances that appear in the maternal circulation. However, no such toxic products have been isolated. Many investigators have tried, without success, to demonstrate a vasopressor or antidiuretic substance in the blood of pre-eclamptic women. Hofbauer[2] first suggested that the secretion of the posterior lobe of the pituitary gland might be the cause of pre-eclampsia. Dieckmann[1] states that patients with pre-eclampsia show a rise in blood pressure after injections of Pituitrin; this does not take place in renal or vascular disease. Page[3] injected 400 cc. of blood from women with eclampsia and severe pre-eclampsia into normal pregnant women, who showed no rise in blood pressure or unusual symptoms. Dieckmann[1] confirmed this experiment. The ischemic theory has promising possibilities; it is compatible with overdistention of the uterus. However, other factors must be involved.

The signs and symptoms of pre-eclamptic toxemia are an increase of the blood pressure (especially diastolic) over pre-existing levels and the appearance of albuminuria in the last trimester of pregnancy. In the great majority of cases, these findings are preceded by a marked increase in weight from fluid retention. One still sees an occasional case of "dry eclampsia," which usually occurs in very young primiparas and is a virulent form that rapidly develops into coma and convulsions. These patients apparently do not have fluid retention or a post-partum diuresis.

Sixty to 70 per cent of all pregnant women have some form of fluid retention or visible edema, or both. The most common form is the dependent edema of the legs, largely mechanical in origin owing to increased venous pressure. It is not important in relation to the development of pre-eclamptic toxemia. Edema of the face, hands and abdominal wall is of more significance in relation to pre-eclampsia. The most serious of all types is fluid retention in the extravascular tissue space, which may or may not be accompanied by clinical edema. This can only be judged by weight gain.

Pre-eclampsia does not develop in all women who retain fluid, although such patients are most prone to pre-eclampsia. There is as yet no method of determining which women will become toxic and which will not. Therefore, it is essential to treat all such women as cases of potential toxemia. In the average patient fluid retention can be well controlled by a proper diet. If it is not controlled, it shows either that the patient is not on the proper diet or that toxemia may be developing.

The hypertension in pre-eclampsia must be judged by a different standard from that of essential hypertension and renal disease. The diastolic pressure is the more important index. A systolic pressure of 140 to 150 may indicate impending eclampsia. A rise in blood pressure to 160 systolic, with a diastolic pressure of over 100, may mean a very sick patient. Patients with renal disease and essential hypertension may have a higher blood pressure without serious trouble.

The amount of albumin in the urine is of definite prognostic significance. The finding of a +++ to ++++ test for albumin indicates advanced toxemia. In the early stages of pre-eclampsia, albumin is the only abnormal finding in the urine. In the severe stage, and in eclampsia, casts and red blood cells may appear in the sediment. There is no demonstrable change in renal function in mild pre-eclampsia.

Early pre-eclampsia causes very few and sometimes no symptoms. It may be entirely an accidental finding in the physician's office. Lethargy and mild headaches may be the first complaints. As symptoms develop with the progress of the disease, they tend to be cerebral and visual. A frontal headache is the most common. Visual disturbances such as double vision and spots before the eyes are also frequent. Occasionally, blurring or complete loss of vision is the first subjective symptom. The development of symptoms in addition to pre-existing signs is always of serious import. The patient may be rapidly approaching the eclamptic state. This is particularly true of epigastric pain of the girdle type. In patients who have had no prenatal care it is frequently the development of the symptoms that first brings them to the doctor; at this point they may be acutely ill.

In early or mild pre-eclampsia, there is no important change in the blood chemical constituents. In certain areas of poor economic status and diet, patients may show a hypoproteinemia. Correction of this will improve the patient's condition. This does not seem to be a factor in most patients with toxemia. The nonprotein nitrogen is within normal limits. The blood urea nitrogen is low in pregnancy but does not change in toxemia. A rise in the blood uric acid is characteristic of some of the severer forms, but this is not always present. Hematocrit and hemoglobin estimations are usually within normal limits. With the progression to severe pre-eclampsia or eclampsia there may be marked changes in the blood chemical findings as well as signs of renal failure.

The pathology of severe pre-eclampsia and eclampsia is primarily renal, cerebral and hepatic. The typical renal lesion is a glomerulonephrosis, which is apparently secondary rather than primary. This lesion is not found in mild cases but only when the disease is severe. This has been the finding in the Mallory Institute of Pathology, where many cases have been studied. Also in that institution, typical lesions of peripheral hemorrhagic necrosis of the liver have been found in only 50 per cent of all cases of eclampsia. The cerebral pathology consists of cerebral edema, followed in many of the severe cases by macroscopic and microscopic hemorrhage. It is also believed in this institution that there is a characteristic premature aging of the placenta in cases of pre-eclamptic toxemia that is not found in the other hypertensive states. Bartholomew and Colvin[4] describe acute hemorrhagic infarcts of the placenta, which they regard as grossly characteristic of pre-eclamptic eclampsia. I am inclined to agree with their observations. There appears to be a gross differentiation between the old yellow and white infarcts of the placenta in chronic nephritis and the fresh hemorrhagic infarcts in pre-eclamptic toxemia.

The treatment for pre-eclampsia is the prevention of its occurrence. There is no specific treatment for the disease once it has developed except termination of pregnancy. During recent years, with improved prenatal care, and especially, with the realization of the importance of sodium retention, there has been a marked decline in the incidence of pre-eclampsia in most obstetric clinics. In clinics where the patients avail themselves rarely or not at all of prenatal care, pre-eclampsia is still frequently seen.

Dieckmann[1] has demonstrated the importance of sodium retention in the development of pre-eclampsia. The ingestion of large amounts of sodium will rapidly put weight on the normal pregnant woman. Elimination of sodium will reduce this weight gain. Intravenous injection of sodium into the pre-eclamptic woman will cause an increase in the edema and blood pressure, a marked increase in proteinuria and an increase in symptoms. A falling blood pressure in definite relation to the effectiveness of diuresis is a common observation in an obstetric ward. The blood pressure rises again after diuresis if the patient again begins to retain fluid and electrolytes.

The treatment of pre-eclamptic toxemia remains confused and unsatisfactory. The method must be adjusted to the individual case, depending on the severity of the disease, its rate of progression, any underlying renal or cardiac lesion and duration of the pregnancy. The fundamental and primary object of treatment is to cause an elimination of retained fluid. The amount and extent of diuresis is probably the soundest factor on which to base prognosis. The hypertension and albuminuria will respond favorably to any successful diuresis.

Laboratory studies are not of great help in the mild or early case of pre-eclamptic toxemia. The ability of the kidney to concentrate and dilute urine is the most sensitive and helpful test of renal function. Any impairment of this function suggests underlying renal damage and makes the prognosis

more serious. The blood uric acid and serum proteins should be checked. A low protein must be replaced. A rise in uric acid is an indication of pre-eclamptic toxemia. The blood should also be checked for any evidence of anemia, immediate treatment being instituted when indicated.

In discussing treatment of this condition, one must divide the cases into mild and severe. When mild there is sufficient time for treatment and a reasonable expectation of sufficient improvement so that the patient may continue with her pregnancy for a reasonable period. In the severe case, impending eclampsia may force one's hand in a matter of days or sometimes hours. It is well to remember, especially in the mild case, that the duration of pre-eclampsia has a greater influence than its severity on the development of permanent renal or vascular damage. This is perfectly reasonable when one considers that the longer arteriolar spasm is present, the more permanent the change in the vessel walls.

On admission to a hospital, the patient should be put immediately to bed and kept at complete bed rest. A mild sedative is helpful in calming her fear and restlessness. She should be kept as quiet as possible, with a minimum of visitors. A chart of fluid intake and output should be immediately established, and all precautions taken that this is accurately kept. Because of the loss of fluid through the skin and lungs, particularly during hot weather, this chart will not be too accurate, but it should show a negative fluid balance if an efficient diuresis is taking place. A low-sodium diet is instituted, 200 mg. being the lowest practical objective. This diet must be carefully controlled, and all precautions taken that the patient receives no other food. In addition to low sodium, the patient must be given the necessary proteins, minerals and other substances of a well rounded diet.

The question of fluid intake in these patients has been much debated, and there is no common agreement. After many years of restricting fluids, I have changed to giving fluids as desired. No definite clinical change has been noted on the two regimens. The patients are more comfortable on free fluids, which, theoretically, may help flush the retained electrolytes through the kidneys.

Diuretics are a helpful adjunct to treatment. Ammonium chloride is the most commonly used and is both efficient and safe. Mercurial diuretics are also used and appear to be somewhat more efficient. The danger of mercurial diuretics has been overstressed. However, if a patient has definite renal failure, ammonium chloride may be safer.

Under this regimen at the Boston City Hospital, a weight loss of 4 to 6 pounds in three or four days is considered to indicate a good prognosis. Frequently, this weight loss is exceeded in this period. In a week a patient should lose 10 to 15 pounds. The prognosis is based on this daily weight loss, which correlates closely with the regression of the other signs and symptoms. As mentioned above, the actual loss is a more accurate gauge than a chart of fluid intake and output.

A patient who responds promptly to treatment within five days to a week is considered safe to discharge home under careful supervision. She is given a printed list of a proper low-sodium diet. The dangers and warning signs of her condition are explained to her. She is seen at home by the visiting nurse and every few days at the clinic.

Patients with early or mild toxemia generally respond well to treatment; those who do not are reclassified in the severe group and treated accordingly. In the treatment of pre-eclamptic toxemia, one must learn to differentiate the mild and the severe case. Sometimes, this is self evident, and at other times the response to treatment is the deciding factor. The blood pressure can be quite misleading. Patients have gone into convulsions with a systolic pressure of 140 and lower. One must always remember that a mild hypertension may be of serious import in toxemia although not dangerous in the other hypertensive syndromes. A pre-eclamptic toxemia with a blood pressure of over 160 systolic and particularly over 100 diastolic must be considered a serious case. The measurement of the albumin in the urine is important, since large amounts indicate severe toxemia. In addition, the symptoms are extremely significant in the estimation of a given case, any marked cerebral symptoms (severe and persistent headache, mental lethargy and confusion) or blurring or loss of vision being extremely serious. Epigastric pain, particularly of the girdle type, frequently warns of impending eclampsia.

Marked weight gain, with a rapid appearance of signs and symptoms, indicates an acute and fulminating toxemia. In certain primiparas under twenty a severe toxemia may develop, progressing to eclampsia in a few days or a week.

Once a case has been classed as severe pre-eclampsia, the termination of pregnancy may have to be considered. It should be considered immediately if the baby is sufficiently mature to survive.

The method of delivering the patient must depend on the individual case. Time is an important factor. A long, inefficient labor or an unsuccessful induction may precipitate eclampsia. Induction of labor should not be attempted unless the presenting part is well engaged and the cervix most favorable. Since severe toxemia develops in most primiparas and many multiparas before the cervix is favorable for induction, cesarean section is indicated in such cases.

The question whether a patient with severe pre-eclampsia should receive an attempt at medical treatment before the pregnancy is terminated again depends on many factors. There is definite dan-

ger in waiting, and yet in certain cases a patient's condition may be improved by a few days of medical treatment. If disease is of short duration, with rapid progression, immediate termination is probably indicated; if it has progressed slowly and is not too severe a course of medical treatment may be sufficient. It must always be remembered that post-partum eclampsia may develop if the disease has become too acute before delivery.

In addition to bed rest, low-sodium diet, diuretics and sedation, magnesium sulfate has a long and well recognized place in treatment. Primarily effective in lowering hypertension, it may be given intramuscularly in doses of 5 to 10 cc. of a 50 per cent solution. After the initial dose it may be repeated every six hours. This is helpful for temporary use but should not be given for more than a few days.

A great deal of work has been done with *Veratrum viride* and its derivatives, which are effective hypotensive drugs. A reduction of blood pressure can be obtained and maintained over a considerable period. Certain dangers in the use of these drugs must be fully understood, although the active fractions are safer than the crude drug. In a proper environment where the patients can be carefully watched and checked these drugs may be of value in trained hands. Many other hypotensive agents are appearing and are being investigated. However, it must be understood that the lowering of hypertension does not cure pre-eclamptic toxemia. In fact the question of increased anoxemia must be considered, since the hypertension may be a protective mechanism. The whole problem of hypotensive drugs offers much hope but is still an investigative rather than an accepted procedure.

Eclampsia

Eclampsia, or the development of convulsions or coma, or both, is the terminal stage of pre-eclamptic toxemia. The only successful treatment of the disease, again, is its prevention — in other words the pregnancy in patients with severe pre-eclampsia should be terminated before eclampsia develops. The recognition of this fact has caused a marked diminution in the incidence of eclampsia throughout the United States. Also, public realization of the importance of prenatal care has brought most patients to the doctor in time for the preceding pre-eclampsia to be recognized and treated.

In the great majority of cases in which a patient is under observation the physician has sufficient time to recognize and treat an impending toxemia, terminating the pregnancy if necessary, before eclampsia develops. There is still the occasional case of acute fulminating toxemia in which toxemia may develop, convulsions appearing in a few days. It is this type of eclampsia that is still seen. In addition, some patients with no prenatal care still arrive in the hospital in convulsions. The doctor who has a patient under observation for pre-eclampsia and allows eclampsia to develop by delaying the termination of pregnancy is permitting the patient to progress from a condition with a mortality of less than 0.5 per cent into one in which the mortality is from 15 to 25 per cent.

Impending signs of developing eclampsia in the pre-eclamptic patient were mentioned above. Any great rise in blood pressure or increase in albuminuria, headache, visual symptoms, mental confusion, or epigastric pain, especially of a girdle type, constitutes a sign of impending eclampsia. In addition, any patient who does not show definite improvement under hospital treatment is a potential candidate for eclampsia.

In severe pre-eclamptic toxemia and especially in eclampsia, definite signs of renal failure appear. Casts, blood, and large amounts of albumin are present. Anuria and oliguria frequently develop. A rise in nonprotein nitrogen and other changes in blood chemical constituents accompany renal failure. The systolic and diastolic blood pressures rise to high levels. The appearance of convulsions and coma completes the picture. The patient is now critically ill. The more rapid the convulsions and the longer they continue, the more serious the prognosis. Deep coma between convulsions, anuria and pulmonary edema are all of critical import. A rise in temperature, pulse and respirations is an ominous sign.

The immediate treatment of a patient with eclampsia is the control of the convulsions and coma. No immediate attempt at delivery should be made. However, once the convulsions are under control, immediate delivery may be necessary to save the patient's life.

On admission, the patient should be placed in a quiet, cool, dark room. A nurse or doctor should be in constant attendance. Nothing should be given by mouth, and a suction apparatus must be available. The patient should be disturbed as little as possible by examinations or other procedures. 15 mg. (¼ gr.) of morphine should be given immediately. Magnesium sulfate, 5 to 10 cc. of 50 per cent solution, is given intramuscularly. This can be followed in an hour by barbiturates or chloral hydrate. The sedation should be repeated at sufficiently frequent intervals to quiet all restlessness. Administration of magnesium sulfate may be repeated every six hours. Chloroform is still useful in controlling the actual convulsions. Trilene may prove to be a safer substitute. If oliguria is severe or anuria develops, hypertonic dextrose in distilled water may be given intravenously in 5 to 20 per cent solution.

Once the patient has recovered from the convulsions and become relatively conscious, the question of delivery should be considered. In a multipara with a favorable and ripe cervix, rupture of the membranes may be indicated. If this procedure is performed, the medical treatment

must be continued as before. The patient should be allowed to go into labor, with normal or low forceps delivery. If the cervix is unfavorable, and in all primiparas, cesarean section is indicated. After any type of delivery, the medical treatment should be continued over a period of days until the patient is definitely improved.

As shown by Dieckmann[1] the interval between the first convulsion and delivery is extremely important. The longer this interval, the higher the maternal mortality. On the other hand, attempted delivery during the convulsive stage carries the highest mortality. Dieckmann[1] recommends delivery within six to eight hours if possible. However, this interval must be prolonged in certain cases. It is a matter of the best obstetric judgment to decide the safest moment to rupture the membranes or perform a cesarean section as indicated.

In post-partum convulsions, the cause of the disease has already been removed. This is less serious than ante-partum or intra-partum convulsions. The same treatment should be given although the termination of pregnancy has already been accomplished.

References

1. Dieckmann, W. J. *The Toxemias of Pregnancy.* Second edition. 710 pp. St. Louis: Mosby, 1952.
2. Hofbauer, J. Zur Klärung der Pathogenese der Eklampsie. *Zentralbl. f. Gynäk.* 61:2482-2485, 1937.
3. Page, E. W. Effect of eclamptic blood upon urinary output and blood pressure of human recipients. *J. Clin. Investigation* 17:207-218, 1938.
4. Bartholomew, R. A., and Colvin, E. D. Diagnosis of occurrence of toxemia of pregnancy by examination of unknown placenta: study of 100 cases. *Am. J. Obst. & Gynec.* 36:909-927, 1938.

MEDICAL INTELLIGENCE

SPONTANEOUS HEMORRHAGE WITHIN THE RECTUS SHEATH*

Report of a Case

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THE occurrence of hematomas within the rectus sheath, although relatively rare, has been sporadically described in the medical literature since the time of Hippocrates and Galen. Most of the reports[1-4] emphasize the difficulty of accurate preoperative diagnosis and state that this condition is rarely thought of in the differential diagnosis of painful abdominal tumors.

Most of the reported cases have occurred as a result of direct trauma.[1] Critical evaluation of those that were thought to be spontaneous revealed a coincidental occurrence of sudden stress or strain on the abdominal wall. These included coughing, sneezing, sudden turning in bed and coitus. A weakened abdominal wall during pregnancy has also been found to be a cause.[5, 6]

In the case reported below, no external trauma or strain was known to have occurred. The patient, however, suffered from severe hypertension, arteriosclerosis, myocardial damage and complete heart block. It is a distinct possibility that the hemorrhage was due to altered circulatory dynamics in a vessel weakened by atherosclerosis. Cullen and Brödel[2, 3] have also reported a case in which heart disease was assumed to have been an etiologic factor.

Case Report

A 65-year-old woman was admitted to this hospital on April 21, 1953, complaining of dyspnea and edema as well as intermittent pain in the upper abdomen for 15 years. The pain was associated with epigastric distress, but there was no jaundice, reversed peristalsis or relation to food. Recently, a gallbladder series taken by a private physician was reported as negative.

The past history included arteriosclerotic and hypertensive heart disease for at least 15 years, with chronic congestive heart failure necessitating a daily ration of digitalis. Two months before admission the patient became bed ridden because of dyspnea and progressive edema of the lower extremities.

Physical examination showed an obese woman in no acute distress. Examination of the eyes, ears, nose and throat revealed no abnormal findings. The neck veins were somewhat congested, with slow venous pulsations. There was no adenopathy, and the thyroid gland was not enlarged. The thorax was symmetrical. The breasts were pendulous. Except for a few moist inspiratory rales at both bases, the lungs were clear to auscultation and percussion. The heart was enlarged, the border of dullness extending downward and to the left. A definite systolic murmur was heard at the apex. The abdomen was obese, and a well healed scar from a previous hysterectomy was noted. There was no tenderness or rigidity, and no masses or organs were palpable (this was confirmed by several examiners). The lower extremities were moderately edematous.

The blood pressure was 230/120; the pulse was 40 and irregular. An electrocardiogram demonstrated coarse fibrillation, with complete auriculoventricular block, at a rate of 47. A right-bundle-branch block was also present.

Early in the morning after admission an extremely severe tearing pain in the right lower quadrant suddenly developed. There was no associated nausea or vomiting. Fever was of low grade, the temperature running around 100°F. The blood pressure was 230/140; the pulse rate remained at 40 and was irregular. Examination of the abdomen revealed a tender, nonmovable, hard mass about 11 cm. in diameter in the right lower quadrant. The abdominal wall was not rigid.

Urinalysis revealed a +-+ test for albumin and a negative test for sugar, 1 to 3 white blood cells per high-power field, occasional red blood cells and rare epithelial cells in the sediment. Ex-

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amination of the blood disclosed a red-cell count of 3,220,000, with a hemoglobin of 12.5 gm. per 100 cc., and a white-cell count of 5600, with 66 per cent neutrophils, 3 per cent stab forms, 28 per cent lymphocytes, 1 per cent eosinophils and 2 per cent monocytes. A plain film of the abdomen was normal.

The mass grew in size, and within a few hours it reached the dimensions of 13 by 15 cm. No pulsation was felt at any time. Many opinions of the character of this mass were expressed by the medical and surgical staff. The differential diagnosis included volvulus, intussusception, cancer of the cecum with perforation, twisted ovarian cyst and appendiceal abscess. Surgical intervention was deemed imperative.

At operation a low right-rectus-muscle incision was made. The subcutaneous tissues appeared edematous. When the outer rectus sheath was incised a hematoma the size of a grapefruit, containing intermingled muscle and necrotic tissue, was found. The blood clot and necrotic mass were evacuated, and all the oozing points ligated. Despite careful search the inferior epigastric vessels could not be identified. The underlying peritoneum and viscera were normal to inspection and palpation. The wound was packed with Gelfoam, and a drain placed within the rectus sheath. Chromic sutures were used for closure. A few hours after the operation, the dressings were found to be saturated with blood. The source of the bleeding could not be identified. A compress binder was applied. The patient died shortly afterward. Surgical intervention was deemed imperative in spite of the poor general condition of the patient.

Discussion

The preoperative diagnosis of hemorrhage within the rectus sheath can easily be made when a history of violent or direct trauma is elicited.[1] There is confusion, however, when the trauma or strain is trivial. In these cases ovarian cyst, appendiceal abscess, rupture of intestinal neoplasm and other acute abdominal conditions are often diagnosed. Cullen and Brödel[1-3] state that if the hematoma is below the umbilicus the absence of the posterior rectus sheath may permit the blood to accumulate between the muscle and the peritoneum. As a result, peritoneal irritation may occur, making the diagnosis even more difficult.

The usual symptoms consist of the sudden onset of pain in the abdomen, often associated with nausea, constipation, distention and muscular rebound elicited over a suddenly developing and expanding tumor. The rapid change in size particularly should suggest hemorrhage. The borders of the mass are always limited by the rectus sheath no matter what the size of the tumor.

The following maneuver may prove helpful in differentiating a painful intra-abdominal tumor from one within the abdominal wall. The examiner's hand should be firmly placed over the involved area with the patient supine. The patient is then asked to sit up against the examining hand. If the lesion is on the abdominal wall the mass will bulge, and the increased local pressure may produce greater pain. An intra-abdominal mass, on the other hand, will be splinted by the abdominal wall and become less marked or disappear entirely; the pain may also be somewhat ameliorated by pressure. Unfortunately, this maneuver was not attempted in the case reported above, in which no history of trauma or strain could be obtained. The associated hypertension, high pulse pressure and irregular, slow pulse may have so altered the hemodynamics of a major atherosclerotic vessel as to produce a spontaneous rupture.

Summary

The medical literature is reviewed, emphasizing the relative rarity and difficulty of diagnosing spontaneous hemorrhage within the rectus sheath.

A case is reported in which the only cause may have been altered hemodynamics. It is suggested that peripheral arteriosclerosis be added to the possible etiology of this condition.

Attention is called to the necessity of including spontaneous hematomas of the abdominal wall in the differential diagnosis of acute abdominal conditions, and aids to physical diagnosis that may prove helpful are suggested.

References

1. Wohlgemuth, K. Über die subcutane Ruptur des M. rectus abdominis und der Art. epigastrica. (Spontanes Bauchdeckenhämatom.) *Arch. f. klin. Chir.* 122:649-654, 1923.
2. Cullen, T. S., and Brödel, M. Lesions of rectus abdominis simulating acute intra-abdominal condition. II. Hemorrhage into or beneath rectus muscle simulating acute abdominal condition. *Bull. Johns Hopkins Hosp.* 61:317-348, 1937.
3. *Idem.* Lesions of rectus abdominis simulating acute intra-abdominal condition. I. Anatomy of rectus muscle. *Bull. Johns Hopkins Hosp.* 61:295-312, 1937.
4. Halperin, G. Spontaneous haematoma of abdominal wall. *Surg., Gynec. & Obst.* 47:861-863, 1928.
5. Morton, P. C. Spontaneous rupture of deep epigastric vein. *J. A. M. A.* 99:1943, 1932.
6. Werthmann, H. Ein Hämatom in linken geraden Bauchmuskel, einen Ovarialtumor vortäuschend. *Zentralbl. f. Gynäk.* 52:240, 1928.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 39531

PRESENTATION OF CASE

A sixty-nine-year-old former post-office employee entered the hospital complaining of loss of weight and progressive weakness.

The patient had felt well until eighteen months previously, when he noted the gradual onset of weakness of his legs that progressed to the point where, six months before admission, he found it necessary to retire. About three months later the weakness was accompanied by pain in both calves and thighs and the lower back. Relief was obtained only by lying or sitting. About nine months before admission he began to experience some urgency of urination and some burning but no difficulty in starting his stream. He also began to have nocturia (two times). About four months before admission he noted intermittent ankle swelling at intervals of about two weeks. A month later he was examined in another hospital because of "colds in the chest." Physical examination was negative except for dullness and rales at the left-lung base and a blood pressure of 200 systolic, 120 diastolic. The urine had a specific gravity of 1.022 and was otherwise normal. Routine blood studies were normal. A roentgenogram of the chest gave findings in the left lower lobe consistent with bronchiectasis. On a subsequent visit about two weeks later the blood pressure was recorded as 180 systolic, 90 diastolic. Two months before admission the patient began to expectorate yellow or greenish mucoid material, especially at night. He denied orthopnea or dyspnea on effort. About a month later marked anorexia developed, and his weight fell from a normal of 130 to 109 pounds. Despite generalized weakness he had not experienced malaise, nausea, vomiting, diarrhea, fever, chills or night sweats.

He smoked moderately and had been in good health except for a slight cough, "bronchitis" for many years and "arthritis" of both hands.

Physical examination showed a man who appeared chronically ill but was in no acute distress. The neck veins were not distended. The lungs were clear except for some loud, bubbly rales in the left-lung base. The heart was of normal size, with a Grade 2, early systolic murmur. The abdomen was soft but slightly tender over the right epigastrium. No organs or masses were felt. The prostate was two or three times the normal size and firm and symmetrical. Extension of the metacarpophalangeal joints was limited.

The temperature was 100°F., the pulse 100, and the respirations 24. The blood pressure was 150 systolic, 90 diastolic.

The urine had a specific gravity of 1.009 and was negative for albumin, bile and sugar. The sediment contained numerous granular and hyaline casts, 5 to 10 white cells and 3 to 5 red cells per high-power field. Bence–Jones protein was absent. Examination of the blood disclosed a hemoglobin of 7.5 gm. per 100 cc., a hematocrit of 26 per cent and a white-cell count of 9000, with 86 per cent neutrophils. The fasting blood sugar was 108 mg., the nonprotein nitrogen 72 mg., and the total protein 5.5 gm. per 100 cc., with an albumin-globulin ratio of 1.0; the sodium was 132 milliequiv., the chloride 95 milliequiv., the potassium 7.0 milliequiv., and the carbon dioxide 25 milliequiv. per liter. The stool guaiac test was negative. Sputum cultures grew out beta-hemolytic streptococci on several occasions and also *Escherichia coli*. Blood culture (two flasks) was negative. An electrocardiogram revealed a sinus rhythm with a rate of 70 and some auricular premature systoles, a PR interval of 0.16 second and a QRS interval of 0.08 second. The P waves were normal, the R waves were fair sized, the T waves and ST segments normal in Lead 1 and the T waves peaked in Leads 2, 3, aVF, V_5, V_6, V_8 and V_9. X-ray films of the bones were negative for metastases. A plain film of the chest demonstrated cystic areas in the left lower lobe and lingula consistent with bronchiectasis (Fig. 1). A gastrointestinal series disclosed a rounded, smooth filling defect measuring 1.5 cm. in diameter at the midportion of the lesser curvature. No other intrinsic disease was seen in the duodenal cap or small bowel. A second gastrointestinal series confirmed the defect seen previously in the stomach. Barium-enema examination was negative.

From the time of admission the patient went gradually and steadily downhill. A bone-marrow biopsy revealed lack of hyperplasia of the erythroid series (myelocyte-erythrocyte ratio of 5:1), with abundance of stored iron. A blood smear showed a normocytic, normochromic anemia but was otherwise not remarkable. A bronchoscopic examination was negative except for the finding of purulent sputum coming from the orifices of the basilar segments of the left lower lobe. Shortly after admission the patient was started on penicillin, strepto-

mycin and sulfadiazine. Later on he received potassium iodide, which was discontinued because of vomiting and a vesiculopustular dermatitis. Urine cultures grew out nonhemolytic streptococci and later on *Pseudomonas aeruginosa* (*Bacillus pyocyaneus*) and abundant *Proteus vulgaris* (*B. proteus*). A cystoscopic examination failed to give evidence of obstruction to urinary flow, and a retrograde pyelogram was normal, with good filling of the calyceal

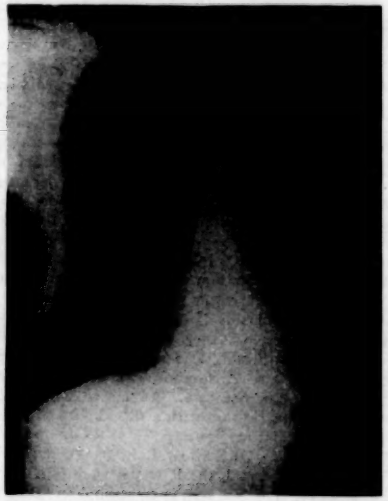

FIGURE 1. *Roentgenogram of the Chest, Showing Extensive Cystic Bronchiectasis of the Left Lower Lobe and Lingula.*

system and renal pelves. Separate urine specimens taken from the ureters grew out a few *Esch. coli* on both sides. In nine subsequent urine examinations, the specific gravity was above 1.010 only once, when it was 1.020; two specimens gave a ++ test for albumin, but the others were negative. The sediment was variable, on one occasion being considered negative; more often, however, it contained occasional to 2 to 10 white cells per high-power field. The greatest number of white cells, 30 to 50, were found one day after cystoscopy, when there were a similar number of red cells. Casts and red cells were otherwise not noted in routine urinalyses, after the admission urine specimen. However, on the twenty-seventh hospital day (two days after cystoscopy) a consultant who examined the urine found a trace of albumin, and 3 to 6 red cells, 10 to 30 white cells, many coarsely granular casts and a rare hyaline cast per high-power field. The stool guaiac test was negative on four occasions and positive on another. The patient was given several transfusions, and the hemoglobin ranged from 5.5 to 8.5 gm. per 100 cc., and the hematocrit from 25 to 34 per cent. The white-cell count rose by the twenty-fourth hospital day to 21,000, with 78 per cent neutrophils, but later fell to 10,000 and was 13,000 two days before death. On the fifteenth, twentieth, twenty-fourth, twenty-seventh, thirty-seventh and forty-first hospital days the serum nonprotein nitrogen was 104, 120, 50, 94, 104, and 160 mg. per 100 cc. respectively. The alkaline phosphatase was 6.6 units on the twelfth and 16.7 units per 100 cc. on the thirty-seventh hospital day. The sodium and chloride did not vary markedly from the normal; however, the carbon dioxide reached 18 milliequiv. and the potassium 7.0 milliequiv. per liter. Other studies included a Congo-red test, which showed 65 per cent retention in the serum, a serum lipase of 0.4 cc., a serum iron of 110 gamma per 100 cc. and a urinary urobilinogen of 0.5 Ehrlich units. A tuberculin skin test was negative in a dilution of 1:100,000; a lumbar puncture was also negative.

The temperature curve was irregular throughout most of the hospital stay, with frequent elevations to 101 or 102°F. Although during the first month the blood pressure was about the same as that on admission, it subsequently tended to be higher, with an average of about 180 systolic, 100 diastolic, and on the thirty-ninth hospital day was recorded by the nurse as 185 systolic, 90 diastolic. The urine output averaged about 750 cc. a day. Terminally, the appetite became poor, and vomiting increasingly frequent until finally nothing taken by mouth could be retained. The patient had diarrhea and became lethargic and confused. He died quietly on the forty-fourth hospital day.

DIFFERENTIAL DIAGNOSIS

DR. MARIAN W. ROPES*: One obvious fact about this case is that many systems were involved — the renal, the skeletal, probably the nervous, the vascular, the pulmonary, the gastrointestinal and the hemopoietic, with an anemia. The skin was also involved, but I shall leave that out because I think the dermatitis was associated with the iodine that was administered. One thing certain is that the patient had renal failure, from which he died. What the underlying cause of the renal failure was and how the diseases of the many systems were interrelated are much less certain. It seems probable, from the course and intertwining of the development of the various conditions, that the involvement of many if not all of the systems was related.

Among the various groups of conditions one has to consider in such cases are generalized infections.

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There is no evidence of an acute generalized infection. There were, to be sure, *Esch. coli* in the sputum, which is peculiar unless antibiotics had been given. Although there was no reference to antibiotics, I assume that the patient received them at some time and that the *Esch. coli* in the sputum was secondary to them. In any event I cannot connect it with the generalized disease. One infectious condition that has to be mentioned whenever there is a great deal of renal and pulmonary involvement is tuberculosis; however, although both the renal and pulmonary disease were typical of tuberculosis the remainder of the picture was not. Moreover in a patient as sick as he was, the old tuberculin test even in a 1:100,000 dilution should have been positive.

The second group to consider is cancer. I think a primary gastrointestinal cancer or a pulmonary or prostatic cancer with generalized involvement is very unlikely. I see no evidence for it. A condition like multiple myeloma, however, always has to be considered when severe renal disease and skeletal symptoms are present together. The renal disease, with its relative lack of urinary abnormalities, is consistent with either the renal involvement of myeloma or the amyloidosis secondary to myeloma. The rest of the conditions would not be well explained by it. It is conceivable that he had myeloma and in addition had a superimposed pulmonary disease but it is unlikely. The very low globulin would be extremely unusual, but without any fractionation it does not rule out myeloma. The alkaline phosphatase interests me; I cannot interpret it but I wonder if it puts any more weight on bone disease than I had considered, or on liver disease.

Dr. Bernard M. Jacobson: Won't you say a kind word for the bone marrow?

Dr. Ropes: I am glad you mentioned it. Of course, that is another point against multiple myeloma. I am going to rule multiple myeloma out, but I was trying to include all the factors that might give some weight to it. I can think of no other generalized cancer that I should consider very seriously.

Another generalized disease one must consider is amyloidosis. Ordinarily, when the renal disease is so severe, it is the so-called secondary amyloidosis (if it is at all legitimate to separate the types). Amyloidosis may be secondary to myeloma or tuberculosis, but I have already said that I do not think he had either of those diseases. The secondary form might theoretically have given him the symptoms and signs of renal disease and possibly the gastrointestinal lesion, although I have never heard of an actual ulcer associated with amyloidosis. I think it is very unlikely that this was the disease.

Among the so-called generalized connective-tissue diseases, another group of generalized diseases that must be included, the one I should consider most seriously is polyarteritis nodosa. I always hesitate even to bring up this diagnosis because I think it is brought up far too often, is usually proved not to be the diagnosis and is used too often as an easy term to put on diseases that we cannot explain. Yet many features in this patient are entirely in accord with it. Severe renal disease and hypertension occur in at least 80 per cent of the cases according to most observers. Renal changes with polyarteritis are so varied that it is impossible to say that those in this patient were not consistent with it; to be sure, there were slightly fewer changes in the urine than I should expect, but I am certain that that does not rule out polyarteritis. It is obvious that he had some superimposed renal infection, but I doubt if the whole renal disease was secondary to renal infection. Death from renal failure is common in polyarteritis nodosa. It is reported to be much more frequent in men than in women. Skeletal or nervous involvement or both are found in the disease. I am given very little information about the joint disease. This patient had metacarpophalangeal joints that could not be extended. Chronic low-grade joint disease in polyarteritis is not uncommon. The leg symptoms are hard for me to interpret; they could have been on a vascular, on a neuritic or on a skeletal inflammatory basis. I see no way of differentiating. The great relief from lying down and lack of use puts more weight on the vascular basis; however, the degree of weakness perhaps gives more weight to the neurologic and the pain extending up to the back to the skeletal basis. Perhaps this would be a good time to look at the x-ray films.

Dr. Joseph Hanelin: The principal radiographic findings are in the chest. There is evidence of a severe cystic bronchiectatic process in the lower portion of the left lung chiefly confined to the lower lobe, which is reduced in size (Fig. 1); there is perhaps some bronchiectasis on the right, but this is not very marked and might even be questioned from the available films. An area of density at the apex is probably due to old scarring. The lungs are emphysematous. The heart does not seem particularly enlarged. Approximately six weeks later, six days before death, the heart appears to have increased in size. There is evidence of more retained secretion in the left lower lobe and what may be an area of atelectasis in the medial portion of the right lower lobe. The lesion of the stomach is a very small defect near the lesser curvature above the angle that is probably clinically unimportant; it looks as though it may be a small adenomatous polyp or a leiomyoma. The skeleton is moderately osteoporotic. Of some help perhaps in explaining the leg pain is the extensive calcification of the branches of the femoral arteries in the upper thighs. The arthritis is mild and chiefly hypertrophic. There is no change in the sacroiliac joints that I should interpret as rheumatoid arthritis.

Dr. Ropes: I am afraid the x-ray films do not help. The pulmonary changes are much more

cystic than I had visualized from the record; therefore, it is less likely that they represented a manifestation of polyarteritis nodosa. Pulmonary symptoms such as asthma and bronchitis are common in polyarteritis nodosa. Bronchitis is never specific; usually, the changes are microscopic unless there is also severe asthma. There have occasionally been reports of small areas of consolidation with actual abscess formation and varying amounts of bronchiectatic changes in patients with polyarteritis nodosa in whom the vessel changes were found in the lung. This is not common and is not characteristic of the disease. The stomach changes interest me, in terms of the possible diagnosis of polyarteritis nodosa. I do not know how often ulceration in the stomach has ever been recorded in cases of polyarteritis nodosa. Ordinarily, the ulcerations and the hemorrhagic changes occur in the intestine, but in one series reported from the Mayo Clinic by Wold and Baggenstoss* there were actual small gastric ulcers in the base of which were small vessels with periarterial changes. Whether these were due to the polyarteritis or not I do not know.

To sum this case up I should say that the one definite fact was that the patient had severe renal disease and that he died of renal failure. Of the diseases that might involve all these systems I think that polyarteritis nodosa has more chance of explaining the findings. It seems probable that the pulmonary disease was separate, with slowly developing bronchiectasis and cystic changes.

DR. ARTHUR S. PIER, JR.: Could pyelonephritis alone have caused this?

DR. ROPES: The renal disease could surely have been pyelonephritis. I think he had some renal infection but I tried to relate the diseases in the various systems. It is possible that he had separate involvement of each one of the systems, with at least three or four diseases.

DR. JACOBSON: Do you think the severe anemia could be explained by the renal insufficiency and sepsis?

DR. ROPES: I think the combination of the severe systemic disease and the severe renal disease would explain the anemia.

DR. BENJAMIN CASTLEMAN: For a long time the physicians on the ward considered some form of carcinoma, first of the lung and then of the stomach; after he was in the hospital for a longer time, they got away from that diagnosis. I believe one physician mentioned polyarteritis nodosa.

CLINICAL DIAGNOSES

Probable metastatic carcinoma.
Uremia.
? Polyarteritis nodosa.
Bronchiectasis.

*Wold, L. E., and Baggenstoss, A. H. Gastro-intestinal lesions of periarteritis nodosa. *Proc. Staff Meet., Mayo Clin.* 24:28-33, 1949.

DR. MARIAN W. ROPES' DIAGNOSES

Polyarteritis nodosa, generalized, with renal involvement.
Uremia.
Bronchiectasis.

ANATOMICAL DIAGNOSES

Polyarteritis nodosa, generalized, with marked renal involvement.
Pericarditis, acute, uremic.
Bronchiectasis.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: Autopsy showed that the patient died of renal failure, with a characteristic uremic pericarditis. The lung lesion, as Dr. Ropes predicted, was severe bronchiectasis, involving the left lower lobe and lingula of the upper lobe. Microscopical sections of the kidneys demonstrated many thrombosed arteries in which the elastic tissue was destroyed, and others with so much inflammatory reaction with destruction of the entire wall that aneurysmal out-pocketings were formed — findings very characteristic of polyarteritis nodosa. The kidney parenchyma, as a result of numerous arterial changes, disclosed severe inflammatory reaction throughout — more of a pyelonephritis, although many of the glomeruli were necrotic as well. The arterial changes were not limited to the kidneys, similar findings being found in almost every organ of the body, including the lungs. In the submucosa of the stomach was a vessel with a similar appearance, but I do not believe this was the lesion that was observed on x-ray examination. The arteries in the muscles also had some changes, which may account for some of the weakness of the legs. The prostate showed hypertrophy with some inflammation. The contractions in the hands were Dupreytren's contractures.

DR. JACOBSON: What was the color of the bone marrow?

DR. CASTLEMAN: The bone marrow was quite red and showed hyperplasia of the red-cell elements.

DR. HANELIN: Was the lesion in the stomach identified at autopsy?

DR. CASTLEMAN: No.

DR. BEVERLY W. COBBS, JR.: The question of polyarteritis nodosa did not occur to us until we had given this man iodine the second time (in the form of Priodax) and had seen auricular fibrillation and a precordial rub suddenly develop. We then tardily suspected that he had no ordinary iodine sensitivity. Certainly, in retrospect it seemed to us also that he had quickly become much worse after the first exposure to iodides.

DR. CASTLEMAN: I doubt if the iodism had anything to do with the production of the arteritis,

although the fact that he was hypersensitive may have been a factor in the production of the disease.

DR. ROPES: I should agree that he must have had the arterial changes before he received the iodide, but I also think that such a patient tends to be more sensitive to various drugs.

CASE 39532

PRESENTATION OF CASE

A fifty-five-year-old Negro housemaid was admitted to the hospital because of anorexia, weight loss, weakness and dyspnea.

Ten months previously she first noticed a painless swelling in the region of the submandibular and submaxillary glands. This was associated with a "cold," weakness and a slight weight loss. A roentgenogram of this area gave no evidence of calculi. Nine months before admission she began to cough up a whitish sputum and noted severe dyspnea, without other symptoms, on climbing one or two flights of stairs. Gradually, the cough, exertional dyspnea and weakness increased, and she became anorexic. Eight months later, after several drenching night sweats and a shaking chill, she was admitted to another hospital with the diagnosis of "virus pneumonia" on the right side. She was treated with penicillin, and the temperature fell from 103°F. to normal; she was discharged after ten days although she was told that she should again be hospitalized because of "abnormal findings in the lung" on x-ray examination. Two days before entry she first noted a knifelike pain in the right posterior portion of the chest, made worse by coughing or inspiration. During this ten-month period the masses in the neck had remained about the same size. Her weight had gradually dropped from 145 to 123 pounds. There was no history of edema, hemoptysis, orthopnea or paroxysmal nocturnal dyspnea.

In the past she had always been in excellent health. There was no known exposure to tuberculosis although a year before entry she had worked for a family in which there were 3 cases of "virus pneumonia." She had been born in the British West Indies, coming to the United States at the age of eighteen.

Physical examination showed a chronically ill, tired, elderly-appearing woman with a frequent, sharp nonproductive cough. In the neck there were masses, 3 by 4 cm. and 1 by 2 cm., in the right and left submaxillary areas respectively. In addition lymph nodes varying in size from "a pea to a marble" were palpated in the submandibular, anterior and posterior cervical axillary supraclavicular, inguinal and left epitrochlear regions. In all areas the lymph nodes were firm, nontender, easily movable and not matted together. The skin was clear. The scleras were muddy, and the fundi, although poorly visualized, seemed normal. The neck was supple, and the trachea was in the midline; the thyroid gland not enlarged. The tonsils were moderately hypertrophied. Over the right midlung field posteriorly tactile fremitus was increased, and bronchial breath sounds were present in the same area and at the left-lung base. The heart was not enlarged, the rhythm was regular, and no murmurs were heard. The liver edge was smooth and was palpated 5 fingerbreadths below the right costal margin. The spleen was not felt. Pelvic and rectal examinations revealed no abnormalities, and neurologic examination was negative. Peripheral pulses were normal, and there was no clubbing of the fingers or toes.

The temperature was 99.5°F., the pulse 80, and the respirations 20. The blood pressure was 115 systolic, 80 diastolic.

The urine had a specific gravity of 1.004 and gave a ++ test for albumin. The white-cell count was 4600, with a normal differential. The hemoglobin was 9.5 gm. per 100 cc. The nonprotein nitrogen was 19 mg., the fasting blood sugar 79 mg., the total protein 8.9 gm., the albumin 3.7 gm., the globulin 5.2 gm. with an albumin-globulin ratio of 0.7, the phosphorus 3.4 mg., and the alkaline phosphatase 13.8 units per 100 cc.; the serum calcium was 9.4 milliequiv. per liter. A blood Hinton test was negative. Tuberculin skin tests were negative in the highest strength. A roentgenogram of the chest disclosed bilateral enlargement of parabronchial, paratracheal and paraesophageal lymph nodes (Fig. 1). The mediastinum, though widened, was not displaced. Peripherally the lungs were clear, but there was a small amount of fluid in the right pleural cavity. Roentgenograms of the hands demonstrated no destructive lesions of the bones. On the second hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. RITA M. KELLEY*: May I see the x-ray films?

DR. STANLEY M. WYMAN: The films show considerable cardiac enlargement, probably chiefly of the left ventricle, and a tortuous aorta, which is well seen coming down behind the heart in the overpenetrated film (Fig. 1). There is definite, somewhat lobulated fullness in the mediastinum that is quite consistent with enlarged lymph nodes as noted in the protocol. A suggestion of enlarged lymph nodes is also observed in both hilar regions. A small amount of fluid is present in each pleural space. The esophagus is not remarkable. I see no evidence of splenic enlargement, and the lower border of the liver is not included on the film.

DR. KELLEY: Do you see anything that looks like involvement of the pulmonary parenchyma?

*Assistant in medicine, Massachusetts General Hospital.

DR. WYMAN: There are some linear patchy densities, which I took to be chiefly atelectasis; however, I cannot say that they are not linear mottled infiltrations. I think atelectasis is a more logical explanation; they seem to be limited almost entirely to the lower portion of the lung, as though it was not well aerated.

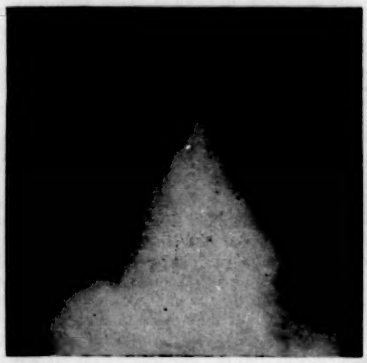

FIGURE 1. *Roentgenogram of the Chest, Showing Bilateral Enlargement of the Hilar Lymph Nodes and Linear Streaking at Both Bases. The left ventricle is enlarged, and the aorta is tortuous.*

DR. KELLEY: Is there consolidation to account for the bronchial breath sounds described over the right-midlung field and the left base?

DR. WYMAN: No; I do not see any appreciable consolidation. The films of the hands are noncontributory.

DR. KELLEY: Was an electrocardiogram done on this woman?

DR. DAVID KAHN: I do not believe so.

DR. KELLEY: I am confronted with a middle-aged woman who had evidence of a chronic progressive disease involving all the peripheral, mediastinal, paratracheal and peribronchial lymph nodes, the liver and probably the pleura and accompanied by certain laboratory changes that were mostly nonspecific but were compatible with a progressive chronic disease with marked systemic changes. Although there was one episode of acute onset of chills, fever, increase in cough and sweating, I gather that these symptoms were not a characteristic feature of the long-term picture, and I am assuming that that was an isolated episode of secondary pneumonia complicating the primary underlying disease. It seems to me that the diagnosis probably lies between a chronic granulomatous process of infectious or unknown nature and a malignant condition involving primarily the reticuloendothelial system.

Among the possible chronic granulomatous diseases are the infectious ones and the nonspecific ones. I am purposely omitting chemically caused granulomatous diseases that might reproduce this clinical picture because there was absolutely no evidence that the patient was carrying on her housemaid's duties within the shadow of a beryllium-belching chimney or something of that sort. Among the infectious processes to be considered are tuberculosis and mycotic infections such as coccidioidomycosis and histoplasmosis. These diseases are described as causing generalized lymphadenopathy at times, but it would be unusual to find such symmetrical and small isolated nodular involvement of the lymph nodes without more definite evidence of intrapulmonary disease or of intermittent fever and chills. In addition there was no information that this patient had inhabited the endemic areas of either coccidioidomycosis or histoplasmosis, so I think I can discount those conditions. If this had been a tuberculous process, it would necessarily have been a protracted type of miliary blood-borne disease, which I should expect to have involved other areas in addition to the lymph nodes and liver. The absence of intrapulmonary disease is against this diagnosis. Also, the process in the lymph nodes, in that it remained isolated and discrete and had no tendency to mat together or break down during the advancing course of the disease, would be most unlike tuberculosis. Moreover, it would be unusual to find a negative or anergic type of tuberculin test in this type of tuberculosis, which is a slow one in contrast to the acute miliary type that may be characterized by a negative tuberculin test. I do not think that this was tuberculosis.

I come to one of two diagnostic choices, either a chronic, so-called granulomatous process such as sarcoidosis of unknown cause or a malignant neoplasm such as one of the malignant lymphomas. Many features of the history, physical findings and laboratory elements are against the textbook picture of either of these categories of diseases. In trying to choose between sarcoidosis and one of the lymphoma group on the basis of history we think of sarcoidosis as an indolent disease characterized by

remissions and exacerbations over a long time. The clinical complaints of the patient are usually much less severe than the pathological picture presented; we are all familiar with cases in which there are no pulmonary symptoms but the x-ray films of the chest show a great deal of involvement of both lymph nodes and pulmonary parenchyma. However, there are in the literature cases of sarcoidosis that have rapidly progressed from the first appearance of symptoms and diagnosis to death in the course of several months. There is therefore a distinct possibility that I am dealing with that kind of nonbenign sarcoidosis. Usually this type of case is characterized by marked pulmonary or cardiac involvement, either primary infiltration of the myocardium with sarcoid nodules or cor pulmonale secondary to advanced pulmonary changes with fibrosis — or both. There was no evidence for the latter type but I am somewhat heartened by Dr. Wyman's description of the enlarged heart because if that was due to sarcoid involvement, it would account for some of the dyspnea, which I cannot explain on the basis of pulmonary disease alone. An electrocardiogram might have been very helpful because the patient who has infiltration of the myocardium with sarcoidosis often shows abnormalities of rhythm with some block, occasionally complete heart block, and transient arrhythmias of various types; however, with a normal pulse that is unlikely. Without other evidence of congestive heart failure, it is improbable that all the dyspnea was on the basis of cardiac involvement alone. In this type of progressive sarcoidosis there have been cases with very pronounced dyspnea and evidence of bronchial compression by involved mediastinal lymph nodes even without infiltration of the lung. This is an unusual occurrence in sarcoidosis. On the other hand, progressive lymphomatous involvement of the mediastinum can easily present as dyspnea, increasing cough, malaise, anorexia and so forth. On the basis of history alone I think that lymphoma wins the round.

The first important physical finding is the disease of the peripheral lymph nodes. The lymph nodes were not very impressively enlarged, except the two submandibular lymph nodes, but in virtually every area they were involved by disease. They were discrete and nontender; the significant point is that their character did not change over the entire ten-month period of the progressive disease. Since I cannot visualize a lymphomatous process that would be so completely static as the disease progressed, I should choose sarcoidosis.

That the liver was enlarged, smooth and nontender is of no particular help in the choice between the two categories because the liver can be involved in either disease. The absence of a palpable spleen somewhat favors sarcoidosis. The lung signs, with bronchial breathing and so forth, which were not confirmed by the x-ray films, again, are not particularly helpful since there may be microscopic pulmonary involvement with either of these processes. Of course, there may be widespread involvement of the mediastinal lymph nodes either in sarcoidosis or in Hodgkin's disease or other lymphomas. The negative findings, including the clear skin and normal heart sounds, do not contribute one way or the other. I should be happier in assigning this to sarcoidosis if the patient had some skin lesions, but they are by no means universal. On the basis of the physical findings I am inclined more to sarcoidosis simply because of the nature of the lymph-node involvement.

In the laboratory data the low specific gravity of the urine and the albuminuria in the presence of a normal nonprotein nitrogen are not helpful since either of these processes can involve the renal parenchyma. The moderately low hemoglobin is against the usual variety of sarcoidosis. This disease, even when it involves the bone, is rarely accompanied by a profound anemia; there is usually normal or a very slight depression of hemoglobin. However, I am trying not to make a diagnosis of the common variety of sarcoidosis, and I think the progressive, severe, what might be called malignant sarcoidosis, particularly, might be accompanied by prolonged anorexia and a low hemoglobin. A hemoglobin of 9.5 gm. per 100 cc., however, is compatible with widespread lymphoma even without bone involvement. The leukopenia, which was not particularly marked, is more in line with sarcoidosis than with an advanced lymphomatous process. Was there any increase in monocytes? Patients with sarcoidosis are often described as having moderate to marked monocytosis, but that again is by no means universal.

DR. KAHN: The blood smear was normal.

DR. KELLEY: The one laboratory finding of any distinguishing character is the total protein and albumin-globulin ratio. A total protein of 8.9 gm. is a definite elevation and was due largely to the

elevation of the globulin fraction to 5.2 gm. There is no question that widespread Hodgkin or other lymphoma, particularly when it involves the liver, can cause a slight hyperglobulinemia, but it would be unusual for the globulin fraction to be that high. I think the hyperglobulinemia favors sarcoidosis, in which it is usually one of the distinguishing characteristics. On the basis of the laboratory findings I think that sarcoidosis is leading by a small margin.

The alkaline phosphatase was definitely elevated; that, too, is not particularly helpful in distinguishing the two pathologic processes. The phosphatase level suggests either intrahepatic disease or extrahepatic obstruction. Either of these diseases can involve the liver directly or cause some obstructive changes.

The next possibly helpful point is the negative tuberculin test. We are all taught that the tuberculin test is rarely positive in extensive sarcoidosis, and it has been used as one of the important differential points and one of the points in the argument concerning the etiology of sarcoidosis. On the other hand many patients with lymphoma have a negative tuberculin test; therefore, it does not help. I should not, however, want to call this sarcoidosis if the tuberculin test had been positive.

The x-ray films do not help very much. The involvement of the mediastinal lymph nodes was symmetrical, which can occur in either sarcoidosis or one of the lymphomatous processes. There was no obvious parenchymal lung involvement, which I should like to see if this was diffuse sarcoidosis causing dyspnea to this extent. The normal x-ray film of the hands is not particularly helpful since in many cases of sarcoidosis bony involvement is not demonstrable by x-ray examination; if the findings were positive, I should have another argument on the sarcoid side of the problem.

Balancing up the pros and cons, the tally is nearly equally in favor of either diagnosis. Using two main points as my specific criteria, I am in favor of sarcoidosis. These two points are the nature and changelessness of the lymph nodes over a long period and the hyperglobulinemia. I am visualizing a progressive, severe type of sarcoidosis, with dyspnea, which I must postulate on the basis of compression of the bronchi, possibly myocardial involvement.

DR. ALLEN G. BRAILEY: The fact that this woman was a Negress is in favor of sarcoidosis.

DR. KAHN: I think in the Army series it was seventeen times more common in Negroes than one would expect from population figures.

DR. WILLIAM H. BAKER: I might mention that skin anergy to tuberculin does not differentiate sarcoidosis from lymphoma in view of the fact that it is probably as prominent in Hodgkin's disease and allied lymphomas as it is in sarcoidosis.

CLINICAL DIAGNOSIS

Malignant lymphoma.

DR. RITA M. KELLEY'S DIAGNOSIS

Sarcoidosis.

ANATOMICAL DIAGNOSIS

Sarcoidosis.

PATHOLOGICAL DISCUSSION

DR. KAHN: The operation was a biopsy of an axillary lymph node, which was slightly enlarged. Microscopical examination confirmed Dr. Kelley's diagnosis of sarcoidosis. The lymph node was almost totally replaced by epithelioid cells arranged in a whorled fashion forming tubercle-like structures. A number of giant cells were present. An occasional whorl contained a tiny area of necrosis, but there was no frank caseation. No tubercle bacilli or fungi were found in specially stained sections; guinea-pig inoculations were negative. It is not possible from the histology to predict whether this will turn out to be a rapidly advancing case or pursue a chronic course. We have only a three-week clinical follow-up period on the patient; at that time she felt well, still had some dyspnea and had a hemoglobin of 11 gm. per 100 cc.

DR. WYMAN: I should like to re-emphasize the point that Dr. Kelley brought out: that this x-ray picture may be due to sarcoidosis, to lymphoma or even in some cases to tuberculosis.

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EDITORS GOSSIP

FOUR years ago the American Medical Association abandoned the annual meeting of state-society secretaries and editors in favor of a biennial gathering of editors and business managers of state journals. The second of these conferences took place in November of this year.

This was, as formerly, a two-day meeting, but with a program designed more particularly for the benefit of those physicians and business men and women who are directly concerned with the production of the 34 state, district and territorial publications that benefit from the State Journal Advertising Bureau of the American Medical Association.

As in the past the meeting took place largely under the auspices of the Bureau, which has been such a potent factor in obtaining national advertising for its brood of journals and in maintaining the high ethical standards in advertising that have been established by the councils of the Association.

Without going into details that were not at all tedious for the participants, suffice it to say that the meeting dealt with matters of pharmaceutical advertising and "therapeutic research," with printing problems, including costs and typography, with the responsibilities of medical editorship and with the management of production. As an additional attraction Paul de Kruif, Ph.D., roving editor on matters medical for the *Reader's Digest*, who has at last fallen into the good graces of the American Medical Association, talked entertainingly on his experiences and observations in writing for the public about health and certain ways of seeking it.

The *Journal*, which has been a loyal client of the Bureau and a member of its group since it was first organized, has with regret indicated its decision to pursue an independent course in the procurement of advertising. This change in policy has been the result not of any dissatisfaction with the Bureau or with the councils of the Association, for all of which it has the highest regard, but of a steady growth in circulation that has put it, in respect to its position as a medium for advertisers, in a unique category.

Despite the fact that the Committee on Publications and the editors consider it to be in the best interests of the *Journal* to terminate its business association with the Bureau as of January 1, 1954, they continue to maintain the friendliest relations with the Bureau and to consider themselves as belonging to the group in all except fiscal matters.

SCHOOL VISION TESTS

A SIGNIFICANT forward step to end the confusion that at present surrounds the choice and application of school vision tests was taken recently when the New England Ophthalmological Society and the Section on Ophthalmology and Otolaryngology of the Massachusetts Medical Society, with the cooperation of the Harvard School of Public Health and Children's Medical Center, reported their preliminary recommendations for standards for referral of school children for eye examinations. On the

basis of a questionnaire regarding current standards used by ophthalmologists in their own offices and those advocated in the referral of children for eye examinations, as well as the choice of functions to be tested and of the personnel who should administer the tests and refer the patients, several important considerations were agreed on as a point of departure in the decision of personnel, procedure and the standards themselves.

In the first place it was recommended that a lay person — teacher, nurse or other school personnel — give the vision test; it was not considered desirable to have an ophthalmologist give the test, which is at best but a rough, incomplete examination, since a physician's report of a passing grade might give the parents a false sense of security. Secondly, every child failing the test should be re-examined (by the person who gave the first test or, preferably, by the school nurse or some other specially trained personnel) before being sent home to the parents. Thirdly, the test should be given annually. Finally, it was urged that no note be sent home advising parents of a passing grade, reports being reserved for failure to pass the test and containing that information alone.

Regarding the technic itself, the best procedure in current use was considered to be the Massachusetts Vision Test, which consists of tests for visual acuity, hypermetropia and heterophoria (investigations of stereopsis, color vision and other binocular functions were not recommended for inclusion because they would increase not only the time required but also the complexity of a procedure to be administered by laymen and might lead to an unnecessarily large number of referrals). In addition, it was advised that any child with obvious eye symptoms or reading difficulty be referred for ophthalmoscopic examination, regardless of the results of the visual test.

In passing, it was pointed out that error on the side of too many referrals is always preferable to the opposite of too few. Ophthalmologists were reminded that vision tests are not always accurate and that when a negative examination follows a referral because of a failing grade on the test, it is the duty of the doctor to explain to the parents the value of the eye examination, rather than to give the impression of needless anxiety and inconvenience.

Although the preliminary nature of the recommendations is emphasized in the report, any program to set up uniform standards for referral is welcome. Further progress will be reported from time to time, and any necessary revisions in the recommendations will be made. Meanwhile, the members of the groups participating in the study are congratulated on a noteworthy contribution to the problem of visual tests for school children. It is significant that the National Society for the Prevention of Blindness is incorporating these recommendations in its official report.

THE FRAGILE MALE

It is realized, perhaps somewhat dimly, that women in general live longer than men. The latest figures confirm this impression by indicating that the life expectancy at birth is seventy and a half years for females and sixty-four and seven-tenths years for males. Further confirmation is given by the Bureau of the Census report of July 1, 1948, indicating that there were at that time 446,000 persons eighty-five years of age and older in the United States, 255,000 of whom were females and 191,000 of whom were males.

It is evident that military action, accidents and homicides involve males more frequently than they do females, but the toll of various diseases is also higher in the male. A considerable difference in mortality between the sexes since 1900 has become progressively greater since World War I. In 1926, for example, the death rate for males was approximately 14 per cent higher than that for females, whereas in 1948 the difference had jumped to 41 per cent. Again the death rate from 1940 to 1949 declined 13 per cent for females and only 7 per cent for males. In 1949 the sex differences in mortality were quite definitely in favor of females in every age group.

It seems also that the fragility of the male appears even before birth, for in 1949 about 10,000 deaths occurred in males from congenital mal-

formations, whereas in females there were only about 8000 deaths from the same causes. In many specified diseases the same difference in mortality rate exists. Approximately 800,000 deaths from all causes in 1949 were of males and 600,000 were of females; 25,000 males and 13,000 females died of tuberculosis, 420,000 males and 320,000 females of major cardiorenal diseases, and 22,700 males and 17,300 females of pneumonia and influenza.

Numerous other causes of death — acute poliomyelitis, cancer, ulcer of the stomach and duodenum, appendicitis, accidents, suicide and so forth — show increases in male over female victims. Diabetes and diseases peculiar to females are the main conditions in which the females surpass the males, and in these great progress is being made in prevention.

In Florida, where this statistical analysis (depressing from the male point of view) was compiled,* similar figures are found. In 1949 there were 25,317 deaths, of which 14,974, or about 60 per cent, were of males. There is no intention of deprecating conditions in Florida, but one cannot help wondering about the causal factors — whether males go there to die amid the widely advertised glorious atmospheric conditions, whether dangerous conditions exist in the State, and perhaps even whether the fragile male should invade the State in such multitudes, especially in the winter months.

It seems that nature makes up for all these disasters to the male by arranging for more male babies to be born. In Florida in 1949, for instance, there were 106.2 male births per 100 female births. This rate may be neutralized to some extent, however, by the fact that in 1949 the death rate in the United States for infants under one year of age was 38.3 per 1000 for males and 29.5 per 1000 for females.

The hazards of being a male and living to an age of four score or more years are great, and perhaps the geriatricians should pay greater attention to the fragile male. An alternative would be to insist that the pediatricians carry the weaker sex for a longer period through life!

*Bowden, W. T. Fragile male. *J. Florida M. A.* 38:553, 1952.

CHILDREN'S HOSPITAL SMOOTHS THE WAY

"JOHNNY Goes to the Hospital" is the title of an attractive booklet conceived and distributed by the Public Relations Department of the Children's Hospital in Boston. As the brochure states, the purpose is to acquaint children and parents with the hospital and its procedures, with the object of allaying the anxiety that arises when a family is faced with possible hospitalization. Written for the child in understandable language, and attractively illustrated on each page in color, the pamphlet should do much to calm the fears and dispel the anxiety that arises when the word hospital is mentioned and the sick child is faced with the prospect of leaving home. Not only the child but also the parent can derive much comfort from the depiction of the actual experience of entering a hospital and the description of the procedure in the hospital.

The Public Relations Department deserves much credit for putting forth this booklet, as well as the Accident Handbook that was such a success in 1950. The Handbook has been translated into eight languages and has sold over 1,000,000 copies.

Dr. A. G. Walters, of Pittsburgh, has recently removed a worm, about one-eighth of an inch in length, from the right eye of a patient from Indiana.

Boston M. & S. J. *January 4, 1854*

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

DIAGNOSTIC LABORATORY SERVICES

A new edition of the booklet describing the services of the Diagnostic Laboratory has just been prepared. It is designed to inform doctors and boards of health about the tests performed by the Diagnostic Laboratory, including the newer services, and how they can be utilized effectively. It is available upon application to the Diagnostic Laboratory, 281 South Street, Jamaica Plain.

For the information of physicians and boards of health the telephone of the Diagnostic Laboratory is listed in the telephone directory under the Institute of Laboratories (JA 2-3700). The telephone number for evenings, week ends and holidays, which unfortunately is not listed in the telephone directory, is JA 2-3702. A bacteriologist is in the Laboratory on Saturdays, Sundays and holidays from 9 to 12 noon, at least. In an emergency during other hours, if no answer is obtained, State Capitol Police (CA 7-4600) should be called for telephone numbers of bacteriologists.

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR NOVEMBER, 1953

Résumé

Disease	November 1953	November 1952	Seven-Year Median
Chancroid	5	0	2
Chicken pox	616	1250	862
Diphtheria	3	0	18
Dog bite	886	624	664
Dysentery, bacillary	58	17	5
Encephalitis, infectious	1	0	2
German measles	57	62	62
Gonorrhea	174	126	206
Granuloma inguinale	0	0	0
Hepatitis, infectious	77	96	141†
Lymphogranuloma venereum	1	0	0
Malaria	1	5	5
Measles	36	83	157
Meningitis, meningococcal	9	4	4
Meningitis, Pfeiffer bacillus	5	7	4
Meningitis, pneumococcal	3	1	3
Meningitis, staphylococcal	0	0	0
Meningitis, streptococcal	0	0	0
Meningitis, undetermined	8	4	5
Mumps	931	419	461
Poliomyelitis	74	22	22
Salmonellosis	20	14	8
Scarlet fever	213*	208	290
Syphilis	178	130	183
Trichinosis	5	1	4
Tuberculosis, pulmonary	187	189	196
Tuberculosis, other forms	7	6	10
Typhoid fever	2	1	2
Undulant fever	2	2	2
Whooping cough	164	100	445

*Includes streptococcal sore throat.
†Four-year median.

Comment

Diseases below the seven-year median were chicken pox, diphtheria, measles, scarlet fever and whooping cough.

The 616 cases of chicken pox reported during November made this the lowest figure for this month since 1931.

Two cases of diphtheria reported in November show that it is no longer primarily a cold-weather disease. This is 3 cases less than the 5 reported in October, and equal to the average of 2 for the months of July, August and September.

The 36 cases of measles represented the lowest figure by a considerable margin for the month of November in the history of this state.

With one exception (November, 1952) the 164 cases of whooping cough constituted the lowest figure for the month of November in the history of this state.

Diseases above the seven-year median included bacillary dysentery, infectious hepatitis, meningococcal meningitis, mumps, poliomyelitis and salmonellosis.

The 20 cases of bacillary dysentery reported, although high for the month of November, represented a considerable drop since the peak in the early fall.

Poliomyelitis is persisting late this year, as demonstrated by the fact that the 74 cases reported was the highest number for November since 1927.

Geographical Distribution of Certain Diseases

The following diseases were reported from the communities named:

Diphtheria: Dedham, 1; Fall River, 1; total, 2.

Dysentery, bacillary: Belmont, 1; Billerica, 1; Boston, 24; Cambridge, 10; Danvers, 1; Fitchburg, 1; Ipswich, 1; Lowell, 3; Lynn, 1; Malden, 1; Melrose, 1; Springfield, 1; Tewksbury, 1; Waltham, 4; Watertown, 1; Worcester, 6; total, 58.

Encephalitis, infectious: Haverhill, 1.

Hepatitis, infectious: Athol, 1; Belmont, 3; Boston, 20; Braintree, 2; Brockton, 3; Cambridge, 4; Chelsea, 1; Chicopee, 2; Fort Devens, 2; Framingham, 2; Lowell, 1; Lynn, 5; Middleboro, 2; Newton, 1; North Adams, 2; Northampton, 1; Oxford, 1; Paxton, 2; Plymouth, 4; Quincy, 4; Richmond, 2; Shrewsbury, 2; Somerville, 1; Spencer, 1; Springfield, 1; Worcester, 7; total, 77.

Malaria: Westfield, 1.

Meningitis, meningococcal: Boston, 3; Fall River, 1; Lynn, 1; Quincy, 1; Scituate, 1; Springfield, 1; Wellesley, 1; total, 9.

Meningitis, Pfeiffer bacillus: Boston, 2; Hadley, 1; Plymouth, 1; South Hadley, 1; total, 5.

Meningitis, pneumococcal: Lee, 1; Milford, 1; Pittsfield, 1; total, 3.

Meningitis, undetermined: Chelmsford, 1; Easton, 1; Fall River, 1; Falmouth, 1; Millbury, 1; New Bedford, 2; Worcester, 1; total, 8.

Poliomyelitis: Ashby, 1; Athol, 3; Belchertown, 1; Boston, 5; Brockton, 3; Brookline, 1; Cambridge, 1; Canton, 3; Dedham, 2; Easton, 1; Falmouth, 2; Framingham, 1; Gardner, 1; Great Barrington, 1; Hadley, 1; Haverhill, 2; Holyoke, 1; Hull, 2; Leverett, 1; Lowell, 2; Lynn, 2; Marlboro, 1; Marshfield, 2; Milton, 1; New Bedford, 1; Newton, 1; North Andover, 1; Northampton, 7; North Attleboro, 1; Norton, 1; Peabody, 2; Quincy, 2; Scituate, 1; Seekonk, 1; Somerset, 1; Somerville, 2; Springfield, 2; Stoughton, 1; Waltham, 1; Warwick, 1; Wellesley, 1; Wenham, 1; Westminster, 1; West Springfield, 1; Wilbraham, 1; Winchester, 1; Worcester, 1; total, 74.

Salmonellosis: Attleboro, 1; Bellingham, 1; Boston, 3; Fitchburg, 2; Lowell, 2; Medford, 1; Quincy, 3; Revere, 1; Salem, 1; Somerville, 1; Springfield, 2; Wakefield, 1; Watertown, 1; total, 20.

Trichinosis: Boston, 2; Framingham, 1; Medford, 1; New Bedford, 1; total, 5.

Typhoid fever: Fall River, 2; total, 2.

Undulant fever: Boston, 1; Cambridge, 1; total, 2.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

New Hope for the Retarded: Enriching the lives of exceptional children. By Morris P. and Miriam Pollock. 8°, paper, 176 pp., with 29 illustrations. Boston: Porter Sargent, 1953. $4.50.

This textbook is based on a twenty years' experience with retarded children. It is intended for students and workers in the field of mental health and abnormal child psychology. The preliminary chapters, which discuss the mentally retarded child, are followed by chapters on the authors' program, their curriculum and an extensive presentation for the devices and projects used in their work. There is a special chapter entitled "Teaching 'Speechless' Children to Talk." There is also a list of psychiatric clinics for children. The monograph should be in collections on mental hygiene and mental deficiency. It is a practical book.

Cybernetics: Circular causal and feedback mechanisms in biological and social systems. Transactions of the Ninth Conference, March 20-21, 1952, New York, New York. Edited by Heinz von Foerster. Department of Electrical Engineering, University of Illinois; assisted by Margaret Mead, American Museum of Natural History, New York City, and Hans L. Teuber, Department of Psychiatry and Neurology, New York University College of Medicine. 8°, cloth, 184 pp., with illustrations. New York: Josiah Macy, Jr. Foundation, 1953. $4.00.

Ten papers on various aspects of cybernetics were read at this ninth conference. An appendix lists the references for the papers. The publishing, as usual, is excellent. The series should be in all medical libraries.

Peptic Ulcer: Pain pattern, diagnosis and medical treatment. By Lucian A. Smith, M.D., M.S., assistant professor of medicine, Mayo Foundation, and head of section, Division of Medicine, Mayo Clinic; and Andrew B. Rivers, M.A., M.D., M.S., consultant, Division of Medicine, Mayo Clinic. With a foreword by George B. Eusterman. 8°, cloth, 576 pp., with 208 illustrations. New York: Appleton-Century-Crofts, Incorporated, 1953. $12.50.

The authors, assisted by Drs. Herbert W. Schmidt, C. Allen Good and Richard R. Ferayorni, have presented a thorough discussion of peptic ulcer, with emphasis on treatment. The first chapter is devoted to history from the earliest time to the present. This is followed systematically by chapters on anatomy and pathologic anatomy, physiology, etiology, diagnosis and symptoms and treatment of the disease and its complications. References are appended to the chapters, and there is a good index. The publishing is excellent. The book should be in all collections on gastroenterology.

Pheochromocytoma and the General Practitioner. By Joseph L. DeCourcy, M.D., and Cornelius B. DeCourcy, M.D. 8°, cloth, 165 pp. Cincinnati 2, Ohio. DeCourcy Clinic, 1952.

This monograph discusses pheochromocytoma, the "great mimic," in all its aspects. In support of its nickname 29 cases in which the disease has been mistaken for other conditions are cited. The text begins with a historical résumé, 1886-1952. There is a bibliography of 361 references and an index. The small book should be in all medical libraries.

Mechanisms of Urologic Disease. By David M. Davis, M.D., visiting lecturer in urology, Graduate School of Medicine, University of Pennsylvania. 8°, cloth, 156 pp., with 6 illustrations. Philadelphia: W. B. Saunders Company, 1953. $4.50.

The author of this small book after a long period of teaching and practicing urology, has not attempted to systematize the body of urologic knowledge. His text is organized on the basis of 8 pathologic changes, and he deals with each as it applies to the entire urogenital tract. These conditions are listed as obstruction, infection, stone formation, neoplasm, congenital malformation, trauma, foreign body and neurogenic disorders.

Shame and Guilt: A psychoanalytic and a cultural study. By Gerhart Piers, M.D., staff member, Institute for Psychoanalysis, Chicago, and Milton B. Singer, Ph.D., professor of the social sciences, College of the University of Chicago. With a foreword by Roy R. Grinker, M.D. 8°, paper, 86 pp. Springfield, Illinois: Charles C Thomas, 1953. $3.25. Publication Number 171, American Lecture Series.

This monograph constitutes the first on a psychiatric subject issued in the *American Lecture Series.* The text consists of 2 parts. The first, by Dr. Piers, is a psychoanalytic study of shame and guilt, and the second, by Dr. Singer, discusses shame and guilt cultures. Lists of references are appended to both parts.

Physical Chemistry for Students of Biology and Medicine. By David I. Hitchcock, Ph.D., associate professor of physiology, Yale University School of Medicine. Fourth edition, with laboratory experiments. 8°, cloth, 266 pp., with 31 illustrations. Boston: Little, Brown and Company, 1953. $5.00.

First published in 1932, this standard manual has been revised and brought up to date. New sections have been included in almost every chapter, and diagrams and graphs of experimental data have been added to the text. There is a good index, and the publishing is excellent.

Ciba Foundation Colloquia on Endocrinology. Vol. VI. *Hormonal Factors in Carbohydrate Metabolism.* General editor for the Ciba Foundation, G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch.; assisted by Jessie S. Freeman, M.B., D.P.H. 8°, cloth, 350 pp., with 94 illustrations. Boston: Little, Brown and Company, 1953. $6.75.

This composite book is the joint work of 28 persons. The subject matter includes enzyme systems, the adrenal cortex, insulin and their influence on carbohydrate metabolism, hormonal control of the interconversion of carbohydrate, protein and fat, hormonal control of the storage of glycogen and sex hormones, pregnancy and carbohydrate metabolism. The literature is surveyed, and there are indexes of authors and subjects. The book should be in all collections on the subject.

20 Years of Psychoanalysis: A symposium in celebration of the twentieth anniversary of the Chicago Institute for Psychoanalysis. Edited by Franz Alexander, M.D., and Helen Ross. 8°, cloth, 308 pp. New York: W. W. Norton and Company, Incorporated, 1953. $3.75.

Seven physicians participated in the symposium and read papers on psychoanalysis in relation to medicine, psychiatry, the biologic sciences, social science, psychoanalytic training, and psychoanalysis as a basic science, all presented in the first part of this book. The second part consists of a history of training and research at the Institute. An appendix of 28 pages lists the publications emanating from the Institute, 1932-1952, and the faculty for 1952. The lack of an index detracts from the reference value of the book. It should be in all collections on the subject.

A Bibliography of The World Literature on Blood Pressure, 1920-1950. Edited by Ernest K. Koller and Jacob Katz, Bureau of Applied Social Research and School of Public Health, Columbia University. In 3 volumes. 4°, paper. Vol. I, *Authors and Titles.* Vol. II, *Author Index and Title Index.* Vol. III, *Abstracts.* Boston: Commonwealth of Massachusetts, 1953.

This new bibliography on an important subject is an essential reference tool for all medical libraries. The first volume lists 16,460 articles; the second is a subject-and-author index, and the third consists of approximately 1500 abstracts of selected articles. The publishing is excellent.

Holt Pediatrics. By L. Emmett Holt, Jr., professor of pediatrics, New York University College of Medicine, and director, Children's Medical Service, Bellevue Hospital, New York City; and Rustin McIntosh, Carpentier Professor of Pediatrics, Columbia University College of Physicians and Surgeons, and director of the Pediatric Service in the Babies Hospital, New York City. Twelfth edition. 8°, cloth, 1485 pp., with 269 illustrations. New York: Appleton-Century-Crofts, Incorporated, 1953. $15.00.

This treatise on pediatrics is the joint work of 72 specialists. A bibliography is appended to the various articles, which present current knowledge on the subjects. An appendix is devoted to tables on growth, blood chemistry, renal function, service areas and instructions for parents of diabetic children. There is a good index, and the book is well published. It should be in all medical libraries and in the collections of pediatricians and physicians.

Injuries of the Spinal Cord. Edited by George C. Prather, M.D., and Frank H. Mayfield, M.D. 8°, cloth, 396 pp., with illustrations. Springfield, Illinois: Charles C. Thomas, 1953. $8.75.

This monograph is the joint work of 9 physicians and surgeons. The discussion of the various aspects of spinal-cord injuries is based on a review of the literature of the different phases, including neurosurgical and urologic, nutrition, associated injuries and complications, decubitus ulcers, rehabilitation and psychologic considerations. There is a good index, and the publishing is excellent. The book is recommended for all medical libraries and neurosurgeons.

The Action of Insulin. By Niels Haugaard, Ph.D., assistant professor of physiologic chemistry in research medicine, University of Pennsylvania School of Medicine; and Julian B. Marsh, M.D., assistant professor of physiologic chemistry, Graduate School of Medicine, University of Pennsylvania. 8°, cloth, 113 pp. Springfield, Illinois: Charles C Thomas, 1953. $3.75. (Publication No. 194, *American Lecture Series.*)

The authors present the results of recent investigations into the problem of the mechanism of insulin action. The chapters deal with intermediary metabolism, chemistry of insulin, physiology of insulin action, experimental diabetes, diabetic metabolism, the relation of anterior-pituitary and adrenocortical factors to the action of insulin, the clinical aspects and mechanism of the action of insulin. The literature is thoroughly reviewed, and lists of references are appended to the chapters. There is a good index. The book should be in all collections on diabetes.

NONCLINICAL NOTES

APPOINTMENT OF DR. CASTLEMAN

Dr. Benjamin Castleman, editor of the Case Records of the Massachusetts General Hospital and a member of the editorial board of the *Journal*, has been appointed clinical professor of pathology at Harvard Medical School and chief of the Department of Pathology at Massachusetts General Hospital.

CAMBRIDGE CITY HOSPITAL HEAD

Dr. James F. Collins, former assistant superintendent of the Boston City Hospital, has been appointed medical director of the Cambridge City Hospital. The appointment becomes effective January 4.

NOTICES

EMERY MEMORIAL LECTURE

The E. Stanley Emery Memorial Lecture will be presented by Dr. Cyrus C. Sturgis, professor of medicine, University of Michigan Medical School, in the amphitheater, Peter Bent Brigham Hospital, on Wednesday, January 13, at 8 p.m. The subject will be "The Nature and Treatment of Leukemia and Allied Disorders."

NEW ENGLAND ROENTGEN RAY SOCIETY AND BOSTON ORTHOPEDIC CLUB

There will be a joint meeting of the New England Roentgen Ray Society and the Boston Orthopedic Club in Ware Hall, Boston Medical Library, 8 Fenway, Boston, on Friday, January 15, at 8 p.m.

HARTFORD MEDICAL SOCIETY

A series of lectures sponsored by the Hartford Medical Society will be held in the Hunt Memorial Building, Hartford, Connecticut, on Mondays, at 8:30 p.m. They will be preceded by a clinical conference at one of the local hospitals at 5 p.m.

January 18. The Practical Approach to Treatment of Anxiety. Dr. Joseph F. Hughes, Philadelphia.

February 1. The Surgical Treatment of Pancreatic Disease. Dr. Richard B. Cattell, Boston.

February 15. Some Problems Associated with Major Catastrophes. Dr. I. S. Ravdin, Philadelphia.

March 1. The Diagnosis and Management of Diseases of the Aseptic Meningitis Type. Dr. Theodore E. Woodward, Baltimore.

March 15. Clinical Disturbances Produced by the Overfunction and Underfunction of the Pituitary Gland. Dr. Edward H. Rynearson, Rochester, Minnesota.

April 5. Angiography. Dr. Israel Steinberg, New York City.

April 19. Indications for Surgery in Valvular Heart Disease: With specific reference to mitral stenosis. Dr. Edward F. Bland, Boston.

MASSACHUSETTS HOSPITAL ASSOCIATION

The annual meeting of the Massachusetts Hospital Association will be held at the Hotel Statler, Boston, on Tuesday, January 26. The morning sessions will include panels on emergency planning, improvement of patient care and the problems of hospital reimbursement. The afternoon speakers will be Governor Herter of Massachusetts and Dr. Robert Page, professor of industrial medicine, New York University, and medical director of Standard Oil Company. The dinner speaker will be Dr. Abram L. Sachar, president of Brandeis University.

SOCIETY MEETINGS AND CONFERENCES

JANUARY 6, MARCH 3 and APRIL 21. Massachusetts Society for Research in Psychiatry. Page 750, issue of October 29.

JANUARY 12. Harvard Medical Society. Page 1087, issue of December 24.

JANUARY 13. Boston Gastroenterological Society. Page 1044, issue of December 17.

JANUARY 13. E. Stanley Emery Memorial Lecture. Notice above.

JANUARY 15. New England Roentgen Ray Society and Boston Orthopedic Club. Notice above.

JANUARY 18, FEBRUARY 1 and 15, MARCH 1 and 15 and APRIL 5 and 19. Hartford Medical Society. Notice above.

JANUARY 19. South End Medical Club. Page 1088, issue of December 24.

JANUARY 22, 23, 29 and 30. International College of Surgeons Regional Meeting. Page 828, issue of November 12.

JANUARY 26. Massachusetts Hospital Association. Notice above.

FEBRUARY 2-4. Examination for Public Health Service Medical Officers. Page 750, issue of October 29.

FEBRUARY 5 and APRIL 9. New England Society of Anesthesiologists. Page 914, issue of November 26.

FEBRUARY 15-20. Pan-American Academy of General Practice. Page 790, issue of November 5.

FEBRUARY 23-25. College of Medical Evangelists Alumni Postgraduate Convention. Page 1044, issue of December 17.

MARCH 15-26. Course in Laboratory Diagnosis of Virus Diseases. Page 1044, issue of December 17.

MARCH 27 and 28. American Psychosomatic Society. Page 1044, issue of December 17.

MAY 14-16. Fifth Annual International Group of Doctors in Alcoholics Anonymous. Page 1004, issue of December 10.

MAY 31-JUNE 3. American Urological Association. Page xvii, issue of July 23.

JULY 22 and 23. International College of Surgeons Regional Meeting. Page 828, issue of November 12.

JULY 23-29. International Cancer Congress. Page 914, issue of November 26.

SEPTEMBER 7-10. Nineteenth Annual Congress of the United States and Canadian Sections of the International College of Surgeons. Page 828, issue of November 12.

SEPTEMBER 12-15. Second International Congress of Cardiology. Page 44, issue of July 2.

SEPTEMBER 16-18. American Heart Association Annual Scientific Sessions. Page 44, issue of July 2.

DISTRICT MEDICAL SOCIETIES

ESSEX NORTH

JANUARY 13. Pentucket Club, 111 Main Street, Haverhill.

MAY 12. 113th Annual Meeting. Andover Country Club, Andover.

MIDDLESEX EAST

JANUARY 20. Combined with the Auxiliary.

MARCH 24.

MAY 11. Annual Meeting. (Harlow Dinner.)

MIDDLESEX SOUTH

JANUARY 27. Jenkins Auditorium, Malden High School, Salem Street, Malden. 8:00 p.m.

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, JANUARY 7

THURSDAY, JANUARY 7

*8:00-8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*9:00-10:30 a.m. Cardiac Grand Rounds. Main Amphitheater Children's Medical Center.

*9:00-10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.

10:30-11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*11:00 a.m.-12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.

*5:00-6:00 p.m. Surgical Division Meeting. Mount Auburn Hospital, Cambridge.

*8:15 p.m. Deaconess Medical Lecture. Thyroid Disease. Dr. Lewis Hurxthal. Joslin Auditorium, New England Deaconess Hospital.

FRIDAY, JANUARY 8

*8:00-8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*9:30-11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.

*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.

10:30-11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

12:00 m.-1:00 p.m. Clinicopathological Conference (Boston Floating Hospital). Joseph H. Pratt Diagnostic Hospital.

*12:30-1:30 p.m. Surgery of Upper Genitourinary Tract. Dr. R. Olson. Ward B Classroom, Cambridge City Hospital.

*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.

*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.

*3:00-4:00 p.m. X-ray Conference. Dr. F. Herzan. Ward B Classroom, Cambridge City Hospital.

*4:00-10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Waltham Street.

SATURDAY, JANUARY 9

*8:00-8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*8:30-10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.

*9:00 a.m. Proctology Clinic. Peter Bent Brigham Hospital.

*9:00 a.m. Alcoholism Clinic. Peter Bent Brigham Hospital.

10:30-11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

11:00 a.m.-12:00 m. Blood Clinic. Dr. William Dameshek. Stearns Auditorium, New England Center Hospital.

SUNDAY, JANUARY 10

Your Visit to the Doctor. Nichols Sun Room. Faulkner Hospital, 1153 Centre Street, Jamaica Plain.

(*Notices concluded on page ix*)